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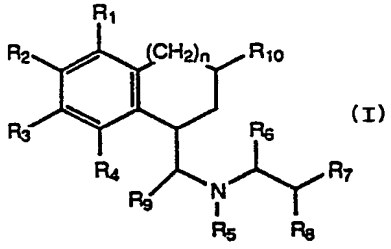

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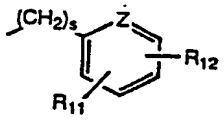

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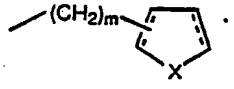

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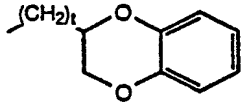

(IV)

(57) Abstract

The present invention includes compounds represented by formula (I), wherein n is 0 or 1; R_1, R_2, R_3 and R_4 are independently selected from hydrogen, hydroxyl, amino, alkylamino, alkylsulfonylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge; R_{10} is independently selected from hydrogen, loweralkyl, phenyl, and substituted phenyl; R_5 is loweralkyl; R_9 is hydrogen or loweralkyl; R_6 and R_8 are hydrogen; and R_7 is (II), wherein m is 0, 1 or 2; X is CH_2, O, S or N-CH_3; or R_7 is (III), wherein s is 0, 1, or 2; Z is C or N; R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is (IV), wherein t is 0 or 1; or R_5 and R_9 taken together form a pyrrolidine ring and then R_6 and R_8 are hydrogen and R_7 is as described above; or R_5 and R_9 taken together form a pyrrolidine ring and then R_6 is hydrogen and R_7 and R_8 taken together may form a phenyl, substituted phenyl, thienyl or furyl ring; or R_5 and R_8 taken together form a pyrrolidine ring and then R_9 and R_6 are hydrogen and R_7 is phenyl, substituted phenyl, thienyl, or furyl; or R_7 and R_9 are hydrogen and R_6 is benzyl, substituted benzyl, thienylmethyl, or furylmethyl; or a pharmaceutically acceptable salt thereof.

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1-AMINOMETHYL-1,2,3,4-TETRAHYDRONAPHTHALENES

Technical Field

This invention relates to alpha-2-adrenergic antagonists useful in the treatment of depression, metabolic disorders (e.g. obesity or diabetes), glaucoma, migraine and hypertension.

Background of the Invention

The adrenergic nervous system plays a major role in the innervation of heart, blood vessel and smooth muscle tissue. Compounds capable of interacting with receptor sites within the adrenergic nervous system can initiate a variety of physiological responses, including vasoconstriction, vasodilation, and increased or decreased heart rate (chronotropic), contractility (inotropic) and metabolic activity. In the past, various adrenergic compounds have been employed to affect these and other physiological responses. However, many adrenergic compounds do not possess significant selectivity to enable desirable interactions with adrenergic receptor sites. That is, these adrenergic compounds do not demonstrate a high degree of specificity for differing receptor types within the

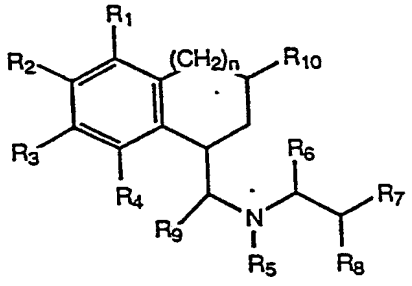
adrenergic nervous system in order to obtain a desired physiological response separate from other possible, and perhaps less desirable, responses of the system.

Disclosure of the Invention

It has now been determined that a new class of compounds, as herein defined, demonstrate an ability to selectively inhibit (antagonists) alpha-2-adrenergic receptors which are mainly distributed on the membranes of central and peripheral adrenergic neurons and on the tissues innervated thereby.

Through inhibitory interaction with the alpha-adrenergic receptor in the peripheral nervous system, one can modulate the function of adrenergic neurons and hemodynamic equilibrium which is therapeutically useful in a multitude of cardiovascular indications such as hypertension, congestive heart failure, and a variety of vascular spastic conditions. Furthermore, the alpha-adrenergic antagonists are useful in certain neurological and psychiatric disorders such as depression.

The present invention includes compounds represented by the formula:



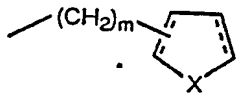
wherein n is 0 or 1;

R_1, R_2, R_3, and R_4 are independently selected from hydrogen, hydroxy, amino, alkylamino, alkylsulfonylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge;

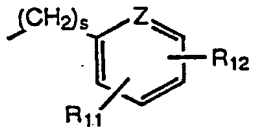
R_5 is loweralkyl;

R_6 and R_8 are hydrogen;

R_7 is

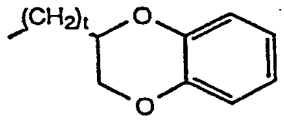


wherein m is 0, 1 or 2 and X is CH_2, O, S or $N-CH_3$; or R_7 is



wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy

or ethylenedioxy bridge; or R_7 is

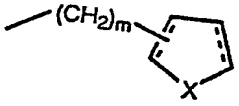


wherein t is 0 or 1;

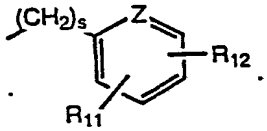
R_9 is hydrogen or loweralkyl; and

R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or

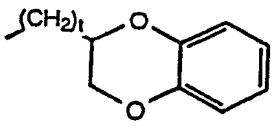
R_5 and R_9 taken together form a pyrrolidine ring and then R_6 and R_8 are hydrogen and R_7 is



wherein m is 0, 1 or 2 and X is CH_2, O, S or $N-CH_3$; or R_7 is



wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is



wherein t is 0 or 1; or

R_5 and R_9 taken together form a pyrrolidine ring and then R_6 is hydrogen and R_7 and R_8 taken together form a phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or

R_5 and R_8 taken together form a pyrrolidine ring and then R_9 and R_6 are hydrogen and R_7 is phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or R_7 and R_9 are hydrogen and R_6 is benzyl, thienylmethyl, furylmethyl or substituted benzyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or a pharmaceutically acceptable salt thereof.

It will be appreciated that the compounds of the present invention contain one or more asymmetric carbon atoms and it is to be understood that the invention includes both the racemic mixture as well as the optically active compounds.

As used in the structures shown above, the dashed lines mean that either a single or double bond may exist.

As used herein, the term "loweralkoxy" refers to alkoxy groups containing 1 or 2 carbon atoms.

As used herein, the term "thioalkoxy" refers to -SR" wherein R" is a loweralkyl residue.

As used herein, the term "loweralkyl" means straight or branched chain saturated hydrocarbon radicals having 1 to 3 carbon atoms, such as methyl, ethyl, n-propyl and iso-propyl.

As used herein, the term "alkylamino" means $-NHR_{20}$ or $-NR_{20}R_{21}$ wherein R_{20} and R_{21} are independently selected from loweralkyl.

As used herein, the term "alkylsulfonylamino" means $R_{22}S(O)_2N(R_{23})-$ wherein R_{22} is loweralkyl and R_{23} is hydrogen or loweralkyl.

As used herein, the term "substituted phenyl" means a phenyl ring with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino, and thioalkoxy.

As used herein, the term "substituted benzyl" means a benzyl group wherein the phenyl ring is substituted with one, two or three substituents independently selected from halo, loweralkoxy, thioalkoxy, loweralkyl, amino and hydroxy.

As used herein, the term "halo" or "halogen" means fluorine, iodine, bromine or chlorine.

The term "pharmaceutically acceptable salts" refers to the pharmaceutically acceptable, relatively nontoxic, inorganic or organic acid addition salts of the compounds of this invention. These salts can be prepared in situ during the final isolation and purification of the compounds, or by separately reacting the free base with a suitable organic or inorganic acid. Representative salts include the hydrochloride, hydrobromide, sulfate, phosphate, nitrate, bisulfate, acetate, oxalate, valerate, oleate, palmitrate, methanesulfonate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napsylate and the like. It will be apparent to those skilled in the art that, depending upon the number of available amino groups for salt formation, the salt of this invention can be per-N-salts.

The compounds of the present invention can be prepared as illustrated in Schemes 1-4.

As seen in Scheme 1, starting with the appropriately substituted 1-tetralone, the dihydro-1-cyanonaphthylene derivative is obtained either with trimethylsilyl cyanide or diethylcyanophosphonate. Reduction to the corresponding aminomethyl tetralin is accomplished with Raney-Nickel to afford compound 1. If desired, the 1-carboxylic acid derivative is obtained after reduction with sodium borohydride, followed by hydrolysis, affording 2.

The amine 1 can be alkylated using the appropriate carboxylic acid or ester, activated ester or acid halide derivatives thereof, followed by reduction of the resulting amide bond. Acid halide derivatives

include the acid chloride. Esters include the methyl and ethyl esters. Activated ester derivatives include activated esters commonly used by those skilled in the art for activating carboxylic acid groups for coupling with an amine to form an amide bond including, but not limited to, formic and acetic acid derived anhydrides, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinimide derived esters, N-hydroxyphthalimide derived esters, N-hydroxybenzotriazole derived esters, 4-nitrophenol derived esters, 2,4,5-trichlorophenol derived esters and the like. In particular, as seen in Scheme 2, compound 1 can be N-alkylated with ethyl formate, followed by diborane reduction of the amide, to give 3 or N-alkylated to the mono ethyl derivative with acetic anhydride, followed by diborane reduction, affording 4.

These secondary amines afford the desired products 5 or 6 upon dicyclohexylcarbodiimide (DCC) promoted coupling with the appropriately substituted carboxylic acids, followed by reduction of the amide intermediates with lithium aluminium hydride. Alkylation to provide 5 or 6 can also be accomplished using carboxylic acid derivatives such as acid halides, esters or activated esters, as described above, followed by reduction of the resulting amide.

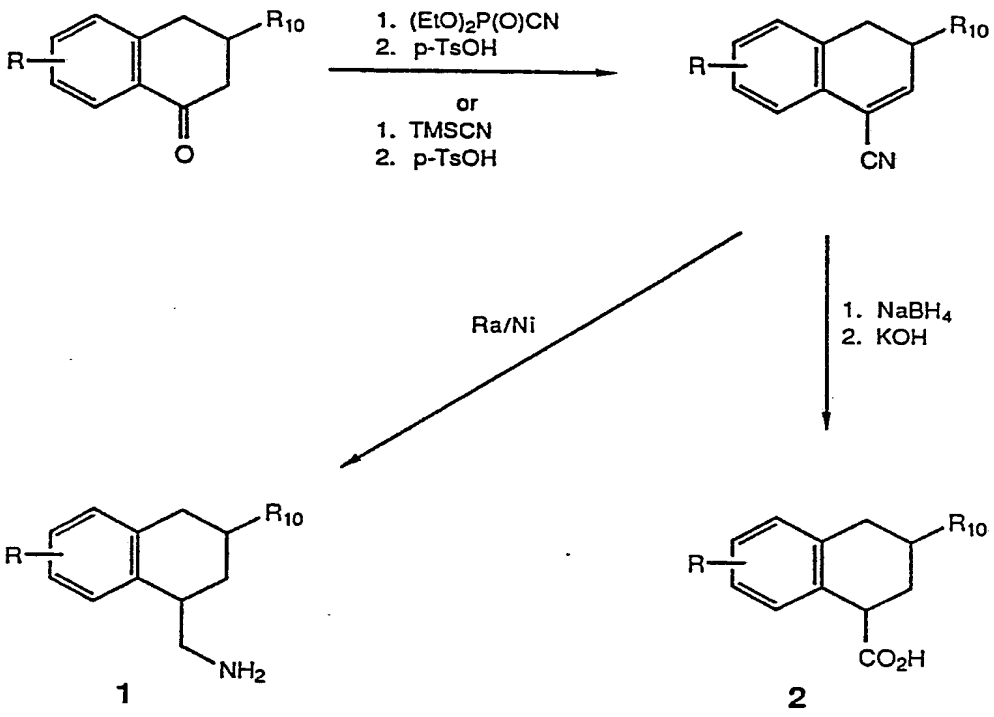
As seen in Scheme 3, compound 2, upon coupling with DCC and the desired pyrrolidine derivative, affords 7 which upon reduction with diborane affords the desired pyrrolidine product 9. Carboxylic acid derivatives such as those described above can also be used in this process.

Alternatively, the pyrrolidine product 12 may be prepared from 2 following formation of the acid chloride with oxalyl chloride and subsequent formation of the carboxamide 8. Treatment of 8 with 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclo-pentane-1-propyl magnesium bromide affords 10 upon reduction with sodium borohydride. N-alkylation of the pyrrolidine is accomplished with DCC coupling with a carboxylic acid derivative and diborane reduction to give 12. Carboxylic acid derivatives such as those described above can also be used in this process.

Compound 8, upon reaction with the desired Grignard reagent and then an appropriately substituted amine in the presence of sodium cyanoborohydride, affords 11. DCC coupling of 11 and the desired carboxylic, acid followed by reduction with either diborane or lithium aluminum hydride, gives the product 13. Carboxylic acid derivatives such as those described above can also be used in this process.

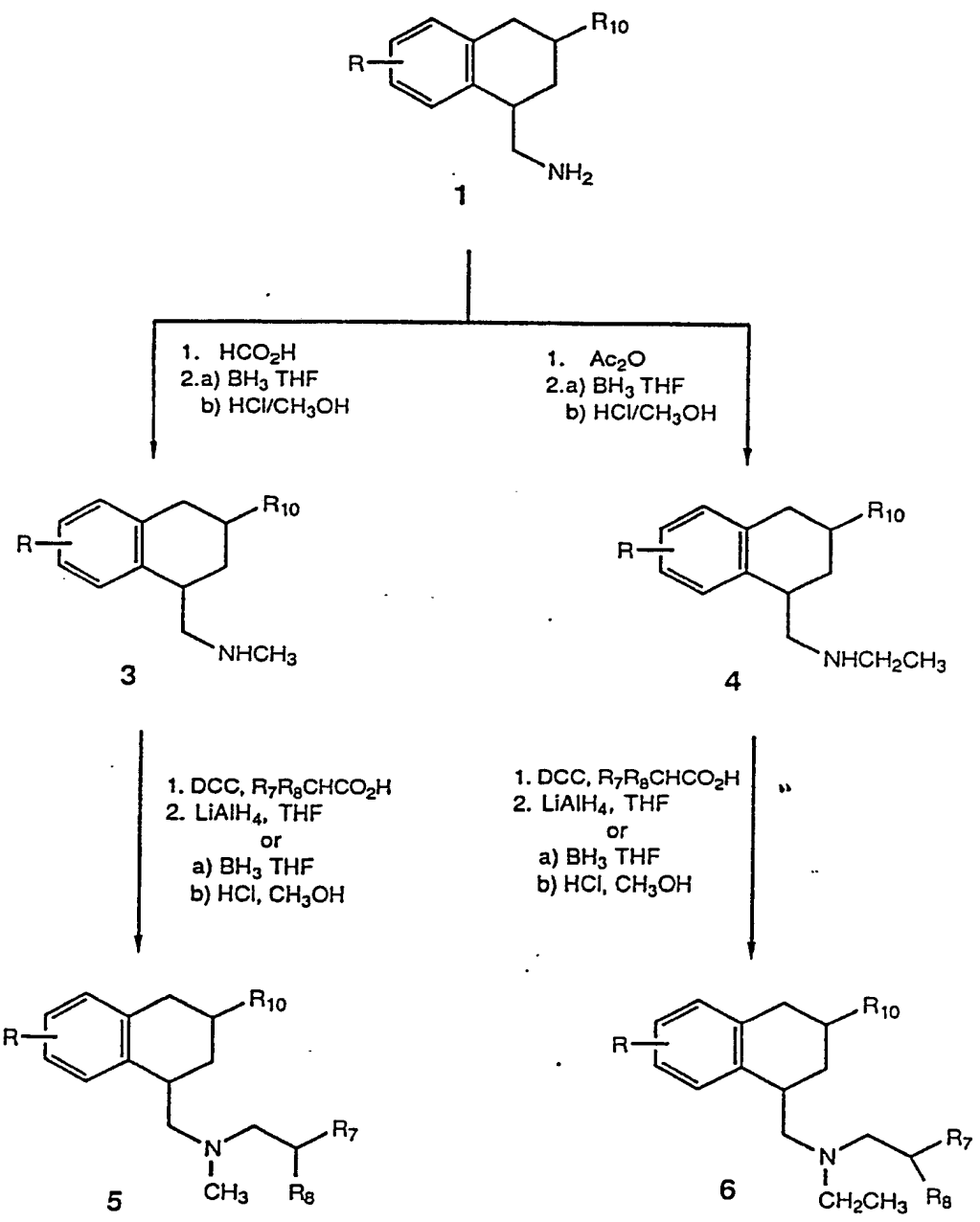
As seen in Scheme 4, the desired 3-substituted 1-tetralones can be synthesized from the appropriate 1,3-dithiane derivative, which is formed from the corresponding substituted benzaldehyde. Addition of the dithiane anion to various cinnamates or acrylates provides the homologated ester. Raney-nickel reduction and basic hydrolysis, followed by acidic cyclization, affords the desired 3-substituted 1-tetralones, which can be carried on as outlined in schemes 1-3.

Scheme 1

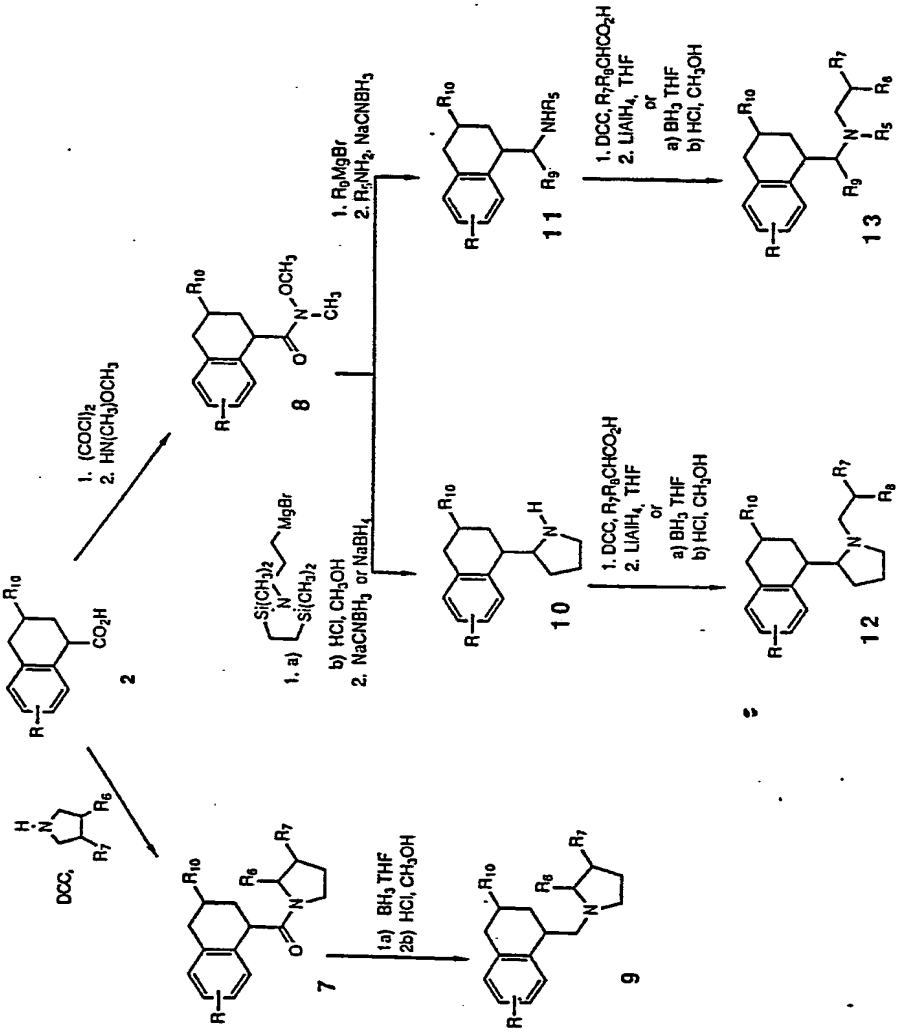

R
R10
O
1. (EtO)2P(O)CN
2. p-TsOH
or
1. TMSCN
2. p-TsOH
CN
Ra/Ni
1. NaBH4
2. KOH
NH2
CO2H

1 2

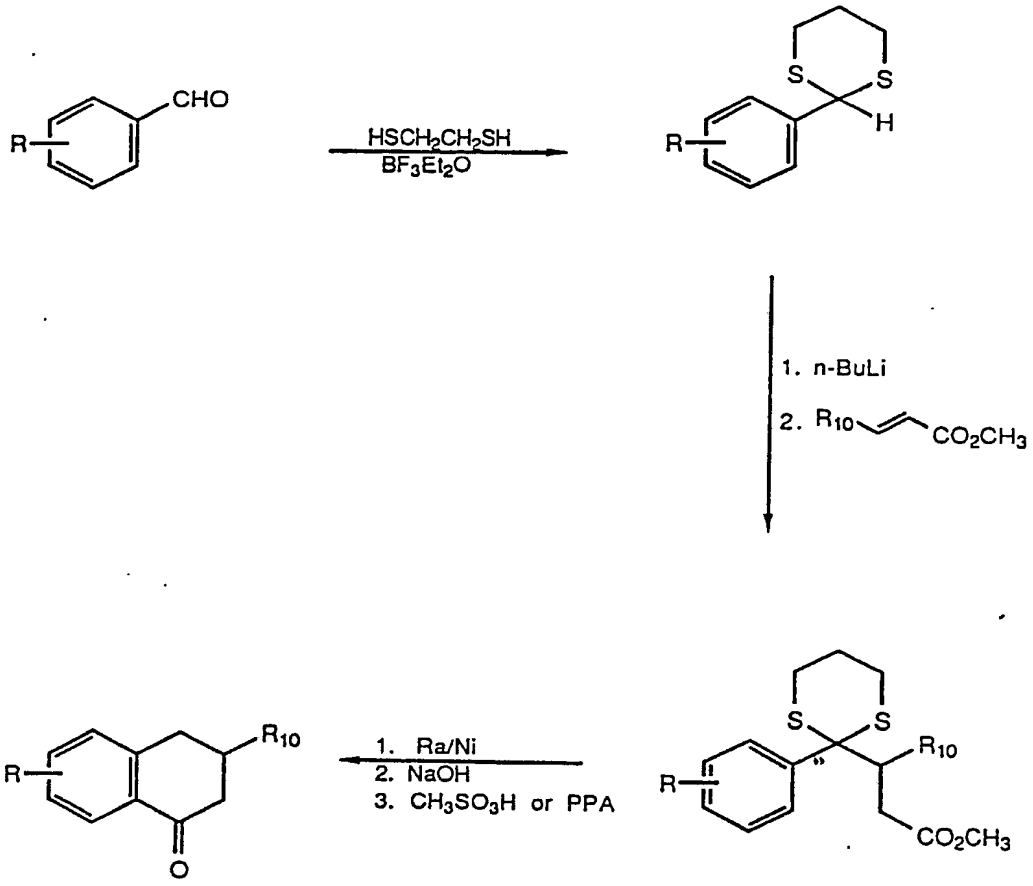
Scheme 2


R
R10
NH2
1
1. HCO2H
2.a) BH3 THF
b) HCl/CH3OH
1. Ac2O
2.a) BH3 THF
b) HCl/CH3OH
NHCH3
3
NHCH2CH3
4
1. DCC, R7R8CHCO2H
2. LiAlH4, THF
or
a) BH3 THF
b) HCl, CH3OH
1. DCC, R7R8CHCO2H
2. LiAlH4, THF
or
a) BH3 THF
b) HCl, CH3OH
N
CH3
R8
R7
5
CH2CH3
6

Scheme 3


1. (COCl)2
2. HN(CH3)OCH3
1. R9MgBr
2. R5NH2, NaCNBH3
1. DCC, R7R8CHCO2H
2. LiAlH4, THF
or
a) BH3 THF
b) HCl, CH3OH
1. a)
b) HCl, CH3OH
2. NaCNBH3 or NaBH4
DCC,
1a) BH3 THF
2b) HCl, CH3OH

Scheme 4


CHO
R
HSCH2CH2SH
BF3Et2O
S
S
H
1. n-BuLi
2. R10
CO2CH3
R10
1. Ra/Ni
2. NaOH
3. CH3SO3H or PPA
O

The foregoing may be better understood in connection with the following examples:

Example 1

1-Cyano-6-methoxy-3,4-dihydronaphthalene

To a refluxing benzene solution (60ml) of 6-methoxy-1-tetralone was added trimethylsilyl cyanide (TMSCN) (67.5g) and a trace of $AlCl_3$ or ZnI_2. Refluxing was continued for 1 hr., then the solvent removed under vacuum. Isopropyl alcohol saturated with HCl(g) was added and the solution refluxed for 1 hr. Precipitation began to occur and the reaction was cooled, then evaporated to dryness. Water was added, followed by an ethyl acetate (EtOAc) extraction. The organic layer was washed in sequence with 1N NaOH, 1N HCl, and brine, separated, dried ($MgSO_4$), filtered and evaporated. The dark oil was chromatographed on silica gel and eluted with CH_2Cl_2, affording 98.5g, 94% yield of product.

Example 2

6-Methoxy-1-aminomethyl tetralin hydrochloride

The product (93g) from Example 1 was hydrogenated at room temperature with RaNi (184g) at 3 atm pressure in the presence of MeOH (900 ml) and NH_3 (100 ml). The solvent was evaporated, H_2O and KOH added, followed by extraction with ethyl acetate. The organic layer was washed with brine, separated, dried ($MgSO_4$), filtered then isopropanol/HCl added. The desired product precipitated, was filtered and dried (87.7g).

Example 3

1-((N-Methylamino)methyl)-6-methoxytetralin hydrochloride

The product from Example 2 was converted to the free base (15g) then dissolved in toluene (40 ml). Ethyl formate (70ml) was added and the reaction refluxed for 2 hr. The solvent was evaporated giving an oil. This was dissolved in dry tetrahydrofuran (THF) (100 ml) and added dropwise to lithium aluminum hydride (3.23 g) in THF, with cooling. Upon complete addition, the reaction was refluxed for 2 1/2 hr. then stirred an additional 24 hr at room temperature, followed by an additional 3 hrs refluxing. The mixture was cooled in an ice bath, then quenched with H_2O (3.3ml), 15% aq. KOH (3.3ml) and H_2O (9.9ml) added dropwise. After stirring for 1 hr at room temperature, the reaction was filtered, and evaporated to dryness. The residue was converted to the HCl salt with ethereal/HCl giving 12.9g desired product.

Example 4

N-(6-Methoxy-1,2,3,4-tetrahydro-1-naphthyl)methyl-N-methyl 2-thienylacetamide

The product from Example 3 was converted to the free base (6g) and dissolved in dry tetrahydrofuran (THF) (125 ml). Then 2-thiopheneacetic acid (3.62g) and 1-hydroxybenzotriazole (5.1g) was added followed by the dropwise addition of N,N'-dicyclohexylcarbodiimide (DCC) 6.7g in dry THF (50ml). The reaction was stirred at room temperature overnight, then filtered and evaporated to dryness. The oil was dissolved in EtOAc and upon standing precipitation occurred. This was filtered, and the filtrate washed with 1N NaOH, then 1N HCl and

brine. The organic phase was dried ($MgSO_4$), filtered and concentrated to afford the product, 7.4 g, 91% yield.

Example 5

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-6-methoxy tetralin methanesulfonate

The product from Example 4 (7.2g) was dissolved in dry THF (50ml) then a 1M solution of BH_3 in THF (65ml) was added dropwise. The reaction was refluxed for 3 hrs., cooled, treated with 6N HCl (50ml) added dropwise, and upon complete addition, refluxed for 2 hrs. The reaction was then allowed to stand overnight during which time a solid precipitated. This solid was filtered and dried giving 7.24g of the hydrochloride salt, m.p. 211-213°C. Anal.calcd. for $C_{19}H_{26}ClNOS$: C, 64.83; H, 7.46; N, 3.98; Found: C, 64.59; H, 7.40; N, 3.74.

The hydrochloride was converted to the free base and dissolved in EtOAc (50ml), then methanesulfonic acid (1.1ml) in EtOAc added. A solid separated, which was filtered giving the product, m.p. 129-30°C. Anal.calcd. for $C_{20}H_{29}NO_4S_2$: C, 58.35; H, 7.12; N, 3.40. Found: C, 58.23; H, 7.01; N, 3.36.

Example 6

Using the product from Example 3 and utilizing the procedures described in Examples 4 and 5 substituting for the 2-thiopheneacetic acid the desired readily available carboxylic acid the following compounds were prepared:

6a) 1-((N-methylamino)methyl-N-(2-(p-fluorophenyl)ethyl))-6-methoxy tetralin hydrochloride; m.p. 202-4°C.

Anal. calcd. for $C_{21}H_{27}ClFNO$: C, 69.30; H, 7.49; N, 3.85. Found: C, 69.07; H, 7.43; N, 3.94.

b) 1-((N-methylamino)methyl-N-(2-(m-fluorophenyl)ethyl))-6-methoxy tetralin hydrochloride; m.p. 203-5°C.
Anal. calcd. for $C_{21}H_{27}ClFNO$: C, 69.30; H, 7.49; N, 3.85. Found: C, 69.32; H, 7.59; N, 3.60.

c) 1-((N-methylamino)methyl-N-(2-phenylethyl))-6-methoxy tetralin hydrochloride; m.p. 206-8°C.
Anal. calcd. for $C_{21}H_{28}ClNO$: C, 72.90; H, 8.17; N, 4.05. Found: C, 72.70; H, 8.01; N, 3.81.

d) 1-((N-methylamino)methyl-N-(2-(3-thienyl)ethyl))-6-methoxy tetralin hydrochloride; m.p. 215-16°C.
Anal. calcd: for $C_{19}H_{26}ClNOS$: C, 64.83; H, 7.46; N, 3.98. Found: C, 64.88; H, 7.62; N, 3.99.

e) 1-((N-methylamino)methyl-N-(4-(2-thienyl)butyl))-6-methoxy tetralin hydrochloride; m.p. 172-5°C.
Anal. calcd. for $C_{21}H_{30}ClNOS$: C, 66.38; H, 7.96; N, 3.69. Found: C, 66.22; H, 7.80; N, 3.24.

f) 1-((N-methylamino)methyl-N-(2-(cyclopentyl)ethyl))-6-methoxy tetralin hydrochloride; m.p. 189-90°C.
Anal. calcd. for $C_{20}H_{32}ClNO$: C, 71.09; H, 9.54; N, 4.14. Found: C, 70.61; H, 9.64; N, 3.97.

g) 1-((N-methylamino)methyl-N-(2-(o-iodophenyl)ethyl))-6-methoxy tetralin hydrochloride; m.p. 140-41°C.
Anal. calcd. for $C_{21}H_{27}ClINO.1/2\ H_2O$: C, 52.46; H, 5.87; N, 2.91. Found: C, 52.34; H, 5.75; N, 2.97.

h) 1-((N-methylamino)methyl-N-(2-(2-tetrahydrothienyl) ethyl))-6-methoxy tetralin hydrochloride; m.p. 163-64°C.

Anal. calcd. for $C_{19}H_{30}ClNSO$: C, 64.11; H, 8.49; N, 3.93. Found: C, 63.52; H, 8.54; N, 3.83.

i) 1-((N-methylamino)methyl-N-(3-(2-thienyl)propyl))-6-methoxy tetralin hydrochloride; m.p. 169-70°C.

Anal. calcd. for $C_{20}H_{28}ClNOS$: C, 65.64; H, 7.71; N, 3.83. Found: C, 65.51; H, 7.42; N, 3.78.

j) 1-((N-methylamino)methyl-N-(3-phenylpropyl))-6-methoxy tetralin hydrochloride; m.p. 169-70°C.

Anal. calcd. for $C_{22}H_{30}ClNO$: C, 73.41; H, 8.40; N, 3.89. Found: C, 73.32; H, 8.57; N, 3.64.

k) 1-((N-methylamino)methyl-N-(2-(m-methoxyphenyl)-ethyl))-6- methoxy tetralin hydrochloride, M^+ 291.

l) 1-((N-methylamino)methyl-N-(2-(m-pyridyl)ethyl))-6-methoxy tetralin dihydrochloride; m.p. 188-89°C.

Example 7

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-6-hydroxy tetralin hydrochloride

The product from Example 4 (2.35g of the HCl salt) was added to CH_2Cl_2 (150ml) and stirred at -78°C while BBr_3 (2.2ml) was added dropwise. Upon complete addition the reaction was allowed to warm to room temperature and stirred for 1 hr. After this period, the reaction was cooled to -78°C and quenched by the careful addition of MeOH. The reaction was

evaporated to dryness then dissolved in MeOH/CH_2Cl_2 and brought to pH7 with NH_4OH. The residue was chromatographed on silica gel and eluted with CH_2Cl_2 with increasing amounts of MeOH to a final concentration of 20% MeOH/80% CH_2Cl_2. The product was evaporated to dryness, dissolved in Et_2O, then ethereal HCl added. Upon evaporation a white solid was obtained which was crystallized from EtOAC-95%EtOH-Et_2O mixture affording the desired product. Anal. calcd. for $C_{18}H_{24}ClNOS$: C, 63.97; H, 7.17; N, 4.15. Found: C, 63.57; H, 7.22; N, 3.98.

Example 8

1-((N-Methylamino)methyl-N-(2-(3-thienyl)ethyl))-6-hydroxy tetralin hydrochloride

Using the compound from Example 6d with the procedure of Example 7 the desired compound was obtained m.p. 114-16°C. Anal. calcd. for $C_{18}H_{24}ClNOS$: C, 63.97; H, 7.17; N, 4.15. Found: C, 63.57; H, 7.22; N, 3.98.

Example 9

1-((N-Methylamino)methyl-N-(2-(p-fluorophenyl)ethyl))-6-hydroxy tetralin hydrobromide

The product from Example 6a (1.6g) was added to CH_2Cl_2 (30ml) then cooled to -78°C. BBr_3 (1.5ml) in 5 ml CH_2Cl_2 was added dropwise, and the reaction was stirred 3 hrs. At the end of this period, MeOH (10ml) was carefully added and the solution was evaporated to dryness affording a brownish residue. This residue was dissolved in CH_3CN and allowed to stand at room temperature overnight. A solid

precipitated and was filtered then recrystallized from CH_3CN affording the desired product, m.p. 129-31°C. Anal. calcd. for $C_{20}H_{25}BrFNO$: C, 60.91; H, 6.40; N, 3.55. Found: C, 60.76; H, 6.42; N, 3.51.

Example 10

1-((N-Methylamino)methyl-N-(2-(m-fluorophenyl)ethyl))-6-hydroxy tetralin hydrochloride

The product from Example 6b (.75g) was O-demethylated with BBr_3 (0.7ml) using the procedure of Example 9. However, after quenching the reaction with MeOH the solution was evaporated to dryness then methanolic HCl (20ml) was added. This was heated on a steam bath until the volume was reduced to ca. 2-3ml. The white solid was triturated with ethylacetate, filtered and dried giving the product, m.p. 154-55°C. Anal. calcd. for $C_{20}H_{25}ClFNO$: C, 68.65; H, 7.22; N, 4.00. Found: C, 68.32; H, 7.22; N, 3.70.

Example 11

1-((N-Methylamino)methyl-N-(2-phenylethyl))-6-hydroxy tetralin hydrobromide

Using the product from Example 6c with the procedure of Example 9 afforded the product, m.p. 156-57°C. Anal. calcd. for $C_{20}H_{26}BrNO$: C, 63.82; H, 6.98; N, 3.72. Found: C, 63.56; H, 6.84; N, 3.46.

Example 12

1-((N-Methylamino)methyl-N-(2-(N-methyl-2-pyrrolyl)-ethyl))-6-methoxy tetralin fumarate

The desired compound (m.p. 145-6°C) was obtained using the procedures of Examples 1-5 but

replacing 2-thiopheneacetic acid with N-methyl-2-pyrrolyl acetic acid and then preparing the fumarate salt in place of the HCl salt. Anal. calcd. for $C_{24}H_{32}N_2O_5$: C, 67.24; H, 7.53; N, 6.54. Found: C, 66.89; H, 7.54; N, 6.26.

Example 13

5-Methoxy-3,4-dihydronaphthalene-1-carbonitrile

5-Methoxy-1-tetralone (8.80g) was dissolved in 50 ml of anhydrous THF and cooled to 5°C under N_2 atmosphere. LiCN (0.50g.) was added to the stirred solution, followed by dropwise addition of diethyl cyanophosphonate (9.1 ml) over 10 min. After 45 min at 5° C., the reaction was poured into 200 ml H_2O and extracted with EtOAc (3 x 100 ml). The combined organic extracts were washed with water (3 x 150 ml), saturated NaCl (150 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The resulting colorless oil was dissolved in benzene (100 ml) and p-toluenesulfonic acid (0.50 g) was added. The reaction was stirred at reflux for 2 hr, cooled to room temperature, and poured into 5% $NaHCO_3$ solution (150 ml). The reaction was extracted with Et_2O (2 x 100 ml) and the combined organic extracts were washed with saturated NaCl solution (150 ml), dried ($MgSO_4$), and evaporated under reduced pressure to yield 9.55 g of a white solid. The product was recrystallized from MeOH to yield 7.81 g of the product as white needles.

Example 14

5-Methoxy-1-aminomethyl-tetralin hydrochloride

The product from Example 13 was hydrogenated

using the procedure of Example 2 to give the desired product. Anal. calcd. for $C_{12}H_{18}ClNO$: C, 63.30; H, 7.91; N, 6.15. Found: C, 63.13; H, 8.15; N, 6.09.

Example 15

1-((N-Ethylamino)methyl)-5-methoxy tetralin hydrochloride

The product from Example 14 was treated with KOH to give the free base, then reacted with acetic anhydride affording the amide. Anal. calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.03; H, 8.25; N, 6.01. This amide was reduced using the procedure of Example 5 to give the desired compound. Anal. calcd. for $C_{14}H_{22}ClNO$: C, 65.74; H, 8.67; N, 5.48. Found: C, 65.71; H, 8.61; N, 5.47.

Example 16

1-((N-Formylamino)methyl)-5-methoxytetralin

The product from Example 14 was converted to its free base (3.4g) and dissolved into toluene (30ml). Ethyl formate (5ml) was added and the reaction stirred at reflux for 5 hr. The solvent was removed to afford a solid. Recrystallization from Et_2O/CH_2Cl_2 afforded 3.07g of desired product. Anal. calcd. for $C_{13}H_{17}NO_2$; C, 71.21; H, 7.81; N, 6.39. Found: C, 71.26; H, 7.82; N, 6.41.

Example 17

1-((N-Methylamino)methyl)-5-methoxytetralin hydrochloride

The product from Example 16 (3.8g) in dry THF (80ml) was treated with 1M solution of BH_3 in THF

(38ml). After the addition was complete, the reaction was heated at reflux for 1hr, followed by cooling. The reaction was treated with saturated methanolic HCl (30ml), heated at reflux for 1 hr and concentrated to afford a solid. Crystallization from Et_2O/CH_3OH afforded 4.1g of desired product. Anal. calcd. for $C_{13}H_{20}ClNO$: C, 64.59; H, 8.34; N, 5.79. Found: C, 64.68; H, 8.49; N, 5.78.

Example 18

N-(5-Methoxy-1,2,3,4-tetrahydro-1-naphthyl)methyl-N-methyl-2-thienylacetamide

The product from Example 17 (1.04g), 1-hydroxybenzotriazole hydrate (1.51g) and 2-thiopheneacetic acid (720mg) in dry THF (30ml) at 0°C was treated with dicyclohexylcarbodiimide (1.16g). The reaction was warmed to room temperature and stirred for 18 hr. The mixture was filtered and concentrated. The residue was dissolved into EtOAc (60ml) washed with 5% aq. HCl (15ml), water (15ml), 10% aq. KOH (15ml), dried ($MgSO_4$) filtered and concentrated. Chromatography on SiO_2 afforded 1.58g of product as a viscous oil.

Example 19

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-5-methoxy tetralin methanesulfonate

The product from Example 18 (1.58g) in dry THF (10ml) was slowly added to a suspension of lithium aluminum hydride (366 mg) in dry THF (30ml) and the resulting mixture heated at reflux for 1hr. The reaction was cooled and treated with water (370uL), 15% aq. KOH (370uL) and water (1.1mL). After 30 min, the

mixture was filtered and the filtrate concentrated. Chromatography on SiO_2 afforded 1.02g of product as a viscous oil. The oil was dissolved into EtOAc(30ml) and treated with a solution of methanesulfonic acid (300uL) in i-PrOH(700uL). Crystallization occurred upon standing to afford 1.17g of desired product, m.p. 178-79°C. Anal. calcd. for $C_{20}H_{29}NO_4S_2$: C, 58.37; H, 7.10; N, 3.40. Found: C, 58.10; H, 7.16; N, 3.39.

Example 20

Using the product from Example 17 and utilizing procedures described in Examples 18 and 19 substituting for the 2-thiopheneacetic acid the desired readily available carboxylic acid the following compounds were prepared:

20 a) 1-((N-methylamino)methyl-N-2-(2-furyl)ethyl))-5-methoxytetralin methanesulfonate, m.p. 154-55°C. Anal. calcd. for $C_{20}H_{29}NO_5S$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.36; H, 7.45; H, 3.52.

b) 1-((N-methylamino)methyl-N-(2-(p-fluorophenyl) ethyl))-5-methoxytetralin methanesulfonate

c) 1-((N-methylamino)methyl-N-(2-(m-fluorophenyl) ethyl))-5-methoxytetralin methanesulfonate, m.p. 180-181°C. Anal. calcd. for $C_{22}H_{30}FNO_4S$: C, 62.39; H, 7.14; N, 3.31. Found: C, 62.36; H, 7.08; N, 3.31.

Example 21

1-((N-Methylamino)methyl-N-(2-(2-furyl)ethyl))-6-methoxy tetralin hydrochloride

Reacting the product from Example 3 with 2-furylacetic acid using the procedures of example 18 gave the desired amide. The amide was reduced using the procedure of example 19 except the hydrochloride salt was prepared with ethereal HCl in place of methanesulfonic acid, affording the compound, m.p. 203-5°C. Anal. calcd. for $C_{19}H_{26}ClNO_2$: C, 67.94; H, 7.80; N, 4.17. Found: C, 67.93; H, 7.90; N, 4.07.

Example 22

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl)) tetralin hydrochloride

The desired compound was prepared (m.p. 222-23°C) using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 1-tetralone. Anal. calcd. for $C_{18}H_{24}ClNS$: C, 67.16; H, 7.51; N, 4.35. Found: C, 66.76; H, 7.82; N, 4.34.

Example 23

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-5,6-methylenedioxy tetralin hydrochloride

The desired compound was prepared (m.p. 248-49°C) using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 5,6-methylenedioxy-1-tetralone. Anal. calcd. for $C_{19}H_{24}ClNO_2S$: C, 62.38; H, 6.57; N, 3.83. Found: C, 62.06; H, 6.57; N, 3.56.

Example 24

1-((N-Methylamino)methyl-N-(2-(m-methoxyphenyl)ethyl))-5,6-dimethoxy tetralin hydrochloride

The product was obtained (m.p. 160-61°C) using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 5,6-dimethoxy-1-tetralone, and using 3-methoxyphenylacetic acid, in place of 2-thiopheneacetic acid. Anal. calcd. for $C_{23}H_{32}ClNO_3$: C, 68.05; H, 7.95; N, 3.45. Found: C, 68.07; H, 7.99; N, 3.24.

Example 25

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-6,7-dimethoxy tetralin hydrochloride

The product was obtained (m.p. 149-50°C) using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 6,7-dimethoxy-1-tetralone. Anal. calcd. for $C_{20}H_{28}ClNO_2S$: C, 62.89; H, 7.39; N, 3.67. Found: C, 62.87; H, 7.23; N, 3.54.

Example 26

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-6,8-dimethoxy tetralin hydrochloride

The product was obtained (m.p. 210-12°C) using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 6,8-dimethoxy-1-tetralone. Anal. calcd. for $C_{20}H_{28}ClNO_2S$: C, 62.89; H, 7.39; N, 3.67. Found: C, 62.55; H, 7.50; N, 3.51.

Example 27

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-7-methoxy tetralin hydrochloride

The product was obtained (m.p. 180-1°C) using

the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 7-methoxy-1-tetralone. Anal. calcd. for $C_{19}H_{26}ClNOS$: C, 64.84; H, 7.45; N, 3.98. Found: C, 64.74; H, 7.28; N, 3.88.

Example 28

1-((N-Methylamino)methyl-N-(2-phenylethyl))-7-methoxy tetralin hydrochloride

The product was prepared (m.p. 178-79°C) using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 7-methoxy-1-tetralone, and using phenylacetic acid, in place of 2-thiopheneacetic acid. Anal. calcd. for $C_{21}H_{28}ClNO$; C, 72.92; H, 8.16; N, 4.05. Found: C, 72.27; H, 8.09; N, 3.87.

Example 29

5,6-Ethylenedioxy-1-tetralone

5,6-Dihydroxy-1-tetralone (6g) was heated at 125°C with 1,2 dichloroethane (7ml) and K_2CO_3 (14g) in DMSO (70ml) under N_2 for 45 min. The reaction was quenched with ice water then extracted with Et_2O. The aqueous layer was removed, then EtOAc added to the remaining organics. This solution was dried ($MgSO_4$), filtered and evaporated to give the desired product.

Example 30

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-5,6-ethylenedioxy tetralin hydrochloride

The product was prepared (m.p. 205-6°C) using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with the product from Example 29. Anal. calcd. for $C_{20}H_{25}ClNO_2S$: C, 63.39; H, 6.65; N, 3.70. Found: C, 62.96; H, 6.99; N, 3.66.

Example 31

6-Thiomethyl-1-tetralone

6-Hydroxy-1-tetralone (16.2g) prepared from 6-methoxy-1-tetralone and $AlCl_3$, was dissolved in dry dimethylformamide (DMF)(50ml) and added dropwise to a suspension of 4g NaH (60% in mineral oil) and dry DMF (200 ml) over 30 min. Then, dimethylthiocarbamyl chloride (14.8g) was added and the reaction heated at 85°C for 4 hrs. The reaction was poured onto ice and extracted with CH_2Cl_2 (150ml). The CH_2Cl_2 layer was washed with 10% aq. NaOH, then saturated NaCl solution. The organic layer was separated, dried (Na_2SO_4), filtered and evaporated giving a tan solid (18.1g). This was added to mineral oil (100 ml) and heated at 270°C for 2 hrs, then cooled. Cyclohexane (500ml) was added and a solid separated (14.3g). This product was added to NaOH (10g) and MeOH (150ml) and refluxed 2 hrs. The reaction was cooled, then methyliodide (9.94g) was added followed by refluxing for 2 hrs. The solvents were removed affording the desired product (11g), M^+192.

Example 32

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-6-thiomethyl tetralin hydrochloride

The product was prepared (m.p. 206-7°C) using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with the product of Example 31. Anal. calcd. for $C_{19}H_{25}ClNS_2 \cdot 1/2\ H_2O$: C, 60.69; H, 6.97; N, 3.73. Found: C, 60.76; H, 7.12; N, 3.64.

Example 33

1-((N-Methylamino)methyl-N-(2-(m-fluorophenyl)ethyl))-5,6-dimethoxy-8-methyl tetralin hydrochloride

The product was obtained (m.p. 184-86°C) using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 5,6-dimethoxy-8-methyl-1-tetralone and using 3-fluorophenylacetic acid, in place of 2-thiopheneacetic acid. Anal. calcd. for $C_{23}H_{31}ClFNO_2$: C, 67.72; H, 7.66; N, 3.43. Found: C, 67.31; H, 7.88; N, 3.37.

Example 34

1-((N-Methylamino)methyl-N-(2-(m-fluorophenyl)ethyl))-5,6-dihydroxy-8-methyl tetralin hydrobromide

Using the product of Example 33 and the procedure of Example 9 the desired compound was obtained m.p. (129-30°C). Anal. calcd. for $C_{21}H_{27}BrFNO_2 . 1/2H_2O$: C, 58.20; H, 6.40; N, 3.23. Found: C, 58.45; H, 6.33; N, 3.02.

Example 35

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-5,6-dimethoxy-8-methyl tetralin hydrochloride

The product was obtained (M^+359) using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 5,6-dimethoxy-8-methyl-1-tetralone.

Example 36

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-5-methoxy-8-methyl tetralin hydrochloride

The product was obtained (m.p. 205-7°C) using

the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 5-methoxy-8-methyl-1-tetralone. Anal. calcd. for $C_{20}H_{28}ClNOS$: C, 65.64; H, 7.71; N, 3.83. Found: C, 65.36; H, 7.90; N, 3.77.

Example 37

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-5-methoxy indane hydrochloride

The product was obtained (m.p. 197-99°C) using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 5-methoxy-1-indanone. Anal. calcd. for $C_{18}H_{24}ClNSO$: C, 63.98; H, 7.16; H, 4.15. Found: C, 64.36; H, 7.19; N, 4.00.

Example 38

6-Methoxy-7-methyl-1-tetralone

3-Methoxy-4-methylbenzoic acid (30g) was reduced to the benzylic alcohol with BH_3 in THF (181 ml of 1M solution). Oxidation of this product (28.7g) with pyridinium chlorochromate (71g) gave the benzaldehyde derivative (21.3g). Treatment of this aldehyde (19.6g) with $BrPh\ P(CH\ )\ COOH$ (54.5g) under Wittig conditions afforded 4-(3-methoxy-4-methylphenyl)-3-butene carboxylic acid (26.9g). Catalytic reduction of this product followed by polyphosphoric acid (PPA) cyclization gave the desired tetralone.

Example 39

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-6-methoxy-7-methyl tetralin hydrochloride

The product was obtained (m.p. 173-4°C) using

the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with the product of Example 38. Anal. calcd. for $C_{20}H_{28}NOS$: C, 65.64; H, 7.71; H, 3.83. Found: C, 65.47; H, 7.56; N, 3.66.

Example 40

1-((N-Ethylamino)methyl)-6-methoxy tetralin hydrochloride

Using the product of Example 2 and the procedure of Example 15 afforded the desired compound.

Example 41

1-((N-Ethylamino)methyl-N-(2-(2-thienyl)ethyl))-6-methoxy tetralin hydrochloride

Using the product of Example 40 and the procedures of Examples 4 and 5 gave the desired compound m.p. 184-85°C. Anal. calcd. for $C_{20}H_{28}ClNOS$: C, 65.64; H, 7.71; N, 3.83. Found: C, 65.48; H, 7.75; N, 3.79.

Example 42

1-((N-Ethylamino)methyl-N-(2-(m-fluorophenyl)ethyl))-6-methoxy tetralin hydrochloride

Using the product of Example 40 and the procedure of Examples 4 and 5 replacing 2-thiopheneacetic acid with m-fluoroacetic acid gave the desired compound, m.p. 153-54°C. Anal. calcd. for $C_{22}H_{29}ClFNO$: C, 70.37; H, 7.73; N, 3.71. Found: C, 70.37; H, 7.93; N, 3.70.

Example 43

1-((N-Ethylamino)methyl-N-(2-(2-furyl)ethyl))-6-methoxy tetralin hydrochloride

Using the product of Example 40 and the

procedure of Examples 18 and 19, replacing 2-thiopheneacetic acid with 2-furylacetic acid and replacing the methanesulfonic acid with ethereal HCl gave the compound, m.p. 176-7°C. Anal. calcd. for $C_{20}H_{28}ClNO_2$: C, 68.65; H, 8.07; N, 4.00. Found: C, 68.58; H, 8.12; N, 4.00.

Example 44

1-((N-Ethylamino)methyl-N-(2-(3-thienyl)ethyl))-6-methoxy tetralin hydrochloride

Using the product of Example 40 and the procedure of Examples 4 and 5 replacing 2-thiopheneacetic acid with 3-thiopheneacetic acid gave the compound, m.p. 159-60°C. Anal. calcd. for $C_{20}H_{28}ClNOS.1/4\ H_2O$: C, 64.84; H, 7.75; N, 3.78. Found: C, 64.93; H, 7.63; N, 3.77.

Example 45

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-6-methoxy indane hydrochloride

Using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 6-methoxy-1-indanone gave the product, m.p. 176-7°C. Anal. calcd. for $C_{18}H_{24}ClNSO$: C, 63.98; H, 7.16; N, 4.15. Found: C, 63.73; H, 7.22; N, 4.13.

Example 46

6-Chloro-3,4 dihydronaphthalene-1-carbonitrile

Using the procedure of Example 13 replacing 5-methoxy-1-tetralone with 6-chloro-1-tetralone afforded the desired product.

Example 47

6-Chloro-1-aminomethyl tetralin hydrochloride

The product from Example 46 was catalytically reduced with Pt_2O at 4 atms. pressure in EtOH and HCl, affording the desired product.

Example 48

1-((N-Methylamino)methyl)-6-chloro tetralin hydrochloride

Using the product of Example 47 and the procedure of Example 3 gave the desired compound.

Example 49

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-6-chloro tetralin hydrochloride

Using the product from Example 48 and the procedures of Examples 4 and 5 afforded the desired compound, m.p. 233-34°C. Anal. calcd. for $C_{18}H_{23}Cl_2NS$: C, 60.67; H, 6.46; N, 3.93. Found: C, 60.61; H, 6.54; N, 3.90.

Example 50

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl)-6-fluoro-tetralin hydrochloride

Using the procedures described in Example 13, then in Examples 46-48 replacing 6-chloro-1-tetralone with 6-fluoro-1-tetralone gave 1-(N-methylamino) methyl-6-fluoro tetralin hydrochloride. Using this product and following the procedures of Examples 4 and 5 gave the desired compound, m.p. 225-27°C. Anal. calcd. for $C_{18}H_{23}ClFNS$: C, 63.62; H, 6.77; N, 4.12. Found: C, 63.93; H, 7.05; N, 4.11.

Example 51

5-Bromo-1-tetralone

To a benzene solution (60ml) of 4-(o-bromophenyl) butyric acid (5g) was added oxalyl chloride (3.6ml) and the reaction refluxed for 1 1/2 hrs. The solution was evaporated to dryness, the residue was dissolved in CH_2Cl_2 (50ml) then cooled to O°C, followed by the addition of $AlCl_3$ (3.1g). The mixture was stirred at O°C warming to room temperature overnight. The reaction was poured onto ice, then extracted with CH_2Cl_2. The organic layer was separated, washed with 1N NaOH, then brine, separated, dried ($MgSO_4$), filtered and evaporated affording the desired product (4.26g).

Example 52

5-Bromo-1,2,3,4-tetrahydronaphthalene-1-carbonitrile

Using the product from Example 51 (10g) and the procedure of Example 1 gave 5-bromo-3,4 dihydronaphthalene-1-carbonitrile (8.5g). This was reduced to the desired product with $NaBH_4$ (8.5g) in ethanol (165 ml), under reflux conditions for 2 hrs.

Example 53

5-Bromo-1-aminomethyl tetralin hydrochloride

The product from Example 52 (5g) was reduced with diborane as in Example 5 and afforded the desired product after recrystallization from EtOH.

Example 54

1-((N-Methylamino)methyl)-5-bromo tetralin hydrochloride

The product from Example 53 was reacted as in

the procedure described in Example 3 and gave the desired compound, m.p. 224-226°C. Anal. calcd. for $C_{12}H_{17}BrClN$: C, 49.59; H, 5.90; H, 4.82. Found: C, 49.73; H, 5.97; N, 4.81.

Example 55

1-((N-Methylamino)methyl-N-(2-(2-furyl)ethyl))-5- bromo tetralin methanesulfonate

Reacting the product of Example 54 with 2-furylacetic acid using the procedure of Example 4 gave the desired amide. This amide was reduced using the procedure of Example 19 giving the desired compound, m.p. 98-99°C. Anal. calcd. for $C_{19}H_{26}BrNO_4S$: C, 51.35; H, 5.90; N, 3.15. Found: C, 51.75; H, 6.00; N, 3.14.

Example 56

1-((N-Methylamino)methyl-N-(2-(2-furyl)ethyl))-6-bromo tetralin methanesulfonate

Using the procedures described in examples 52-55 but replacing 5-bromo-1-tetralone with 6-bromo-1-tetralone afforded the desired compound, m.p. 95-97°C. Anal. calcd. for $C_{19}H_{26}BrNO_4S$: C, 51.35; H, 5.90; N, 3.15. Found: C, 50.96; H, 5.93; N, 3.06.

Example 57

1-((N-Propylamino)methyl)-6-methoxy tetralin hydrochloride

The product from Example 2 was reacted as in Example 15 but replacing acetic anhydride with propionic anhydride and gave the desired product.

Example 58

1-((N-Propylamino)methyl)-N-(2-(2-thienyl)ethyl))-6-methoxy tetralin hydrochloride

Using the product of Example 57 and the procedure of Examples 4 and 5 gave the compound (amorphous). Anal. calcd. for $C_{21}H_{30}ClNOS.1/4 H_2O$: C, 66.60; H, 8.00; N, 3.64. Found: C, 65.78; H, 7.78; N, 3.59.

Example 59

1-((N-Methylamino)methyl)-N-(2-(2-thienyl)ethyl))-5-fluoro indane hydrochloride

Using the procedures described in Example 13, and 46-48 but replacing the 6-methoxy-1-tetralone with 5-fluoro-1-indanone gave the product, m.p. 200-2°C. Anal. calcd. for $C_{17}H_{21}ClFNS$: C, 62.66; H, 6.50; N, 4.30. Found: C, 62.37; H, 6.45; N, 3.98.

Example 60

5-Hydroxy-6-iodo-1-indanone

5-Hydroxy-1-indanone (1.48g), N-iodosuccinimide (2.25g) and CH_3CN (20ml) were stirred at room temperature overnight. The solution was evaporated to dryness, slurried with EtOAc, then filtered. The filtrate was evaporated to dryness and the solid recrystallized from CH_3CN affording the desired compound (0.92g), m.p. 114-15°C.

Example 61

5-Methoxy-6-iodo-1-indanone

The product of Example 60 was added to methyl ethyl ketone (50ml), K_2CO_3 (5g) and methyl iodide

(5ml) then heated at reflux for 4 1/2 hrs. The reaction was cooled, H_2O added, followed by an EtOAc extraction. The organic layer was separated, washed with brine, dried (Na_2SO_4), filtered and evaporated. Trituration of the residue afforded the desired compound after filtration, m.p. 129-30°C.

Example 62

1-((N-Methylamino)methyl)-N-(2-(2-furyl)ethyl))-5-methoxy-6-iodo indane methanesulfonate

Using the product from Example 61 and the procedures described in Examples 13, 14 and 16-19 replacing 2-thiopheneacetic with 2-furylacetic acid afforded the desired product.

Example 63

1-((N-Propylamino)methyl)-5,6-dimethoxy tetralin hydrochloride

Using the procedure of Example 57 but replacing 6-methoxy-1-tetralone with 5,6-dimethoxy-1-tetralone gave the desired product.

Example 64

1-((N-Propylamino)methyl-N-(2-(p-fluorophenyl)ethyl))-5,6-dihydroxy tetralin hydrobromide

Using the product of Example 63 and the procedures described in Examples 4 and 5 replacing the 2-thiopheneacetic acid with 4-fluorophenylacetic acid gave 1-((N-propylamino)methyl-N-(2-(p-fluorophenyl)ethyl))-5,6-dimethoxy tetralin hydrochloride. This product was reacted as described in Example 9 to give the desired product, m.p. 212-14°C.

Anal. calcd. for $C_{22}H_{29}BrFNO_2$: C, 60.27; H, 6.68; N, 3.20. Found: C, 60.26; H, 6.58; N, 3.19.

Example 65

1-((N-Methylamino)methyl-N-(2-(m-nitrophenyl)ethyl))-tetralin hydrochloride

Using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 1-tetralone and replacing 2-thiopheneacetic acid with 3-nitrophenylacetic acid gave the desired compound.

Example 66

1-((N-Methylamino)methyl-N-(2-(m-aminophenyl)ethyl))-tetralin dihydrochloride

The product from Example 65 (3g) was catalytically reduced with 5% Pd/C at 3 atms. pressure in MeOH (95ml) and $CHCl_3$ (5ml) affording the desired amorphous dihydrochloride. Anal. calcd. for $C_{20}H_{27}Cl_2N.1/2\ H_2O$: C, 63.81; H, 7.78; N, 7.44. Found: C, 63.35; H, 7.67; N, 7.38.

Example 67

1-((N-Methylamino)methyl-N-(2-(m-aminophenyl)ethyl))-6-methoxy tetralin dihydrochloride

Using the product of Example 3 and the procedures of Example 4, 5 and 66 the product was obtained, after recrystallization from EtOAc/EtOH. Anal. calcd. for $C_{21}H_{30}Cl_2N_2O.1/2\ H_2O$: C, 62.05; H, 7.70; N, 6.89. Found: C, 62.15; H, 7.83; N, 6.51.

Example 68

1-((N-Methylamino)methyl-N-(2-(m-aminophenyl)ethyl))-6-hydroxy tetralin dihydrobromide

The product from Example 67 (1.1g) was reacted with BBr_3 (1.4ml) as in the procedure of Example 9 and gave the desired product. Anal. calcd. for $C_{20}H_{28}Br_2N_2O$: C, 61.21; H, 7.46; N, 7.14. Found: C, 60.75; H, 7.45; N, 6.89.

Example 69

1-((N-Methylamino)methyl-N-(2-(m-aminophenyl)ethyl))-6-ethoxy tetralin dihydrochloride

Using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 6-ethoxy-1-tetralone and replacing 2-thiopheneacetic acid with 3-nitrophenylacetic acid gave the nitro derivative which was reduced as in Example 66. The product was obtained as an amorphous solid. Anal. calcd. for $C_{22}H_{32}Cl_2N_2O.1\ 1/2\ H_2O$: C, 62.84; H, 7.93; N, 6.66. Found: C, 63.06; H, 7.82; N, 6.47.

Example 70

1-((N-Methylamino)methyl-N-(2-(m-fluorophenyl)ethyl))-tetralin hydrochloride

Using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 1-tetralone and replacing 2-thiopheneacetic acid with m-fluorophenyl acetic acid gave the desired product, m.p. 198-99°C. Anal. calcd. for $C_{20}H_{25}ClFN$: C, 71.94; H, 7.56; N, 4.20. Found: C, 72.33; H, 7.53; N, 3.86.

Example 71

1-((N-Ethylamino)methyl-N-(2-(2-furyl)ethyl))-5-methoxy tetralin methanesulfonate

Using the product (free base) of Example 15 and the procedures described in Examples 18 and 19 but replacing 2-thiopheneacetic acid with 2-furylacetic acid gave the desired compound.

Example 72

1-((N-Ethylamino)methyl-N-(2-(m-fluorophenyl)ethyl))-5-methoxy tetralin hydrochloride

Using the product (free base) of Example 15 and the procedures described in Examples 18 and 19 but replacing 2-thiopheneacetic acid with m-fluorophenyl acetic acid gave the desired compound, m.p. 177-78°C. Anal. calcd. for $C_{22}H_{29}ClFNO$: C, 69.72; H, 7.73; N, 3.71. Found: C, 69.96; H, 7.96; N, 3.66.

Example 73

1-((N-Ethylamino)methyl-N-(2-(2-thienyl)ethyl))-5-methoxy tetralin hydrochloride

Using the product (free base) of Example 15 and the procedures described in Examples 18 and 19 the desired compound was obtained, m.p. 149-151°C. Anal. calcd. for $C_{20}H_{28}ClNOS$: C, 65.64; H, 7.71; H, 3.83. Found: C, 65.86; H, 8.00, N, 3.84.

Example 74

6-Fluoro-1-aminomethyl-3,4-dihydronaphthalene hydrochloride

6-Fluorotetralone (8.2g), and TMSCN (13.4ml) in 15ml benzene containing a trace of $AlCl_3$ or ZnI_2 was

heated at 60-65°C for 6 1/2 hrs. The reaction was added to Et_2O (50ml) then added dropwise to Et_2O (350ml) containing lithium aluminum hydride (3.8g) under N_2. Upon complete addition, the mixture was gently refluxed for 5 hrs followed by stirring at room temperature overnight. The reaction was quenched by the successive addition of EtOAc (12ml), H_2O (4ml), 15% aq. KOH (4ml) and H_2O (12ml). After the quenching the mixture was stirred at room temperature for 1 hr, followed by the addition of anhydrous Na_2SO_4 with an additional 1/2 hr stirring. The reaction was filtered, ethereal HCl was added to the filtrate and the resulting precipitate filtered affording a product mp 177-83°C. This was added to a isopropyl alcohol saturated with HCl (300ml) and heated for 4 1/2 hrs. The solution was cooled and evaporated to dryness and gave the desired compound, m.p. 200-203°C.

Example 75

6-Fluoro-1-aminomethyl-1,2,3,4-tetrahydronaphthalene hydrochloride

The product from Example 74 was reduced as in Example 2 but replacing the NH_3 with acetic acid and afforded the desired compound, m.p. 236-38°C.

Example 76

1-((N-Isopropylamino)methyl)-6-fluoro-tetralin hydrochloride

The product from Example 75 (1.5g) was added to a solution of acetone (25ml) and MeOH (25ml) then 95% sodium cyanoborohydride (1.32g) was added in portions. The pH of the reaction was adjusted to ca. pH 5 after

complete addition of the $NaBH_3CN$. The reaction was then stirred at room temperature for 8 hrs. The reaction was evaporated to dryness, then dilute HCl and CH_2Cl_2 (50ml) was added. The aqueous layer was separated, basified then CH_2Cl_2 added. The organic layer was separated, dried ($MgSO_4$), filtered and evaporated. The residue was taken up in Et_2O (300 ml) then ethereal HCl added. The resulting precipitate was filtered and recrystallized from EtOAc/MeOH giving the desired compound, m.p. 212-14°C.

Example 77

1-((N-Isopropylamino)methyl-N-(2-(2-furyl)ethyl))-6-fluoro tetralin fumarate

The product (free base) of Example 76 was reacted as described in Examples 18 and 19 but replacing 2-thiopheneacetic acid with 2-furylacetic acid and gave the desired product after formation of the fumarate salt, m.p. 138-39°C. Anal. calcd. for $C_{24}H_{30}FNO_5$: C, 66.80; H, 7.01; N, 3.25. Found: C, 66.36; H, 6.89; N, 3.20.

Example 78

1-((N-Isopropylamino)methyl)-5- fluoro tetralin hydrochloride

Following the procedures described in Examples 74-76 but replacing 6-fluoro-1-tetralone with 5-fluoro-1-tetralone afforded the desired product.

Example 79

1-((N-Isopropylamino)methyl-N-(2-(2-furyl)ethyl))-5-fluoro tetralin methanesulfonate

The product (free base) of Example 78 was treated as described in Examples 18 and 19 but replacing 2-thiopheneacetic acid with 2-furylacetic acid giving the desired compound.

Example 80

1-((N-Methylamino)methyl-N-(2-(1,4-benzodioxan)ethyl))-6,8-dimethoxy tetralin hydrochloride

Starting with 1-((N-methylamino)methyl)-6,8-dimethoxy tetralin and using the procedures described in examples 4 and 5 but replacing 2-thiopheneacetic acid with 1,4-benzodioxanacetic acid gave the desired product, m.p. 210-13°C. Anal. calcd. for $C_{24}H_{32}ClNO_4$: C, 66.42; H, 7..43; N. 3.23. Found: C, 66.29; H, 7.37; N, 3.18.

Example 81

1-((N-Methylamino)methyl-N-(3-phenylpropyl))-6- hydroxy tetralin hydrochloride

Using the product from Example 6j and the procedure of Example 10 gave the desired compound, m.p. 120-122°C. Anal. calcd. for $C_{21}H_{28}ClNO.1/2\ H_2O$: C, 71.07; H, 8.24; N, 3.95. Found: C, 70.86; H, 8.08; N, 3.80.

Example 82

1-((N-Methylamino)methyl-N-(2-(m-hydroxyphenyl)ethyl))-6-hydroxy tetralin hydrochloride

Using the product from example 6k and the procedure described in Example 10 the desired compound

was obtained as an amorphous solid. Anal. calcd. for $C_{20}H_{26}ClNO_2 \cdot 2H_2O$: C, 62.57; H, 7.88; N, 3.65. Found: C, 62.35; H, 7.26; N, 3.43.

Example 83

1-((N-Methylamino)methyl-N-(2-(m-hydroxyphenyl)ethyl))-6-methoxy tetralin hydrochloride

Using the product from Example 3 and the procedure of Example 4 replacing the 2-thiopheneacetic acid with m-acetoxyphenylacetic acid gave the corresponding amide. Using this amide and the procedure described in Example 5 afforded the desired compound as an amorphous solid. Anal. calcd. for $C_{21}H_{28}ClNO_2 \cdot H_2O$ C, 66.39; H, 7.96; N, 3.69. Found: C, 66.59; H, 7.71; N, 3.65.

Example 84

1-((N-Methylamino)methyl-N-(2-(m-fluorophenyl)ethyl))-5,6-dimethoxy tetralin hydrochloride

The product was obtained (m.p. 200-201°C) using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 5,6-dimethoxy-1-tetralone and using 3-fluorophenylacetic acid in place of 2-thiopheneacetic acid, m.p. 200-201°C. Anal. calcd. for $C_{22}H_{29}FClNO_2$: C, 67.08; H, 7.42; N, 3.56. Found: C, 66.69; H, 7.47; N, 3.47.

Example 85

1-((N-Methylamino)methyl-N-(2-(m-fluorophenyl)ethyl))-5,6-dihydroxy tetralin hydrochloride

Using the product of Example 84 and the procedures described in Examples 9 and 10, the desired

compound was obtained, m.p. 158-60°C. Anal. calcd. for $C_{20}H_{25}FClNO_2 \cdot H_2O$: C, 62.57; H, 7.09; N, 3.65. Found: C, 62.41; H, 6.59; N, 3.74.

Example 86

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-5,6-dimethoxy tetralin hydrochloride

Using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 5,6-dimethoxy-1-tetralone gave the product, m.p. 235-6°C. Anal. calcd. for $C_{20}H_{28}ClNO_2S$: C, 62.89; H, 7.39; N, 3.67. Found: C, 62.88; H, 7.68; N, 3.67.

Example 87

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-5,6-dihydroxy tetralin hydrochloride

Using the product of Example 86 and the procedures described in Examples 9 and 10 the desired product was afforded Anal. calcd. for $C_{18}H_{24}ClNO_2S$: C, 61.09; H, 6.84; N, 3.96. Found: C, 61.00; H, 7.14; N, 3.65.

Example 88

1-((N-Methylamino)methyl-N-(2-phenethyl)) tetralin hydrochloride

Using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 1-tetralone and replacing 2-thiopheneacetic acid with 2-phenylacetic acid gave the product, m.p. 207-208°C. Anal. calcd. for $C_{20}H_{26}ClN$: C, 76.05; H, 8.30; N, 4.43. Found: C, 75.77; H, 8.67; N, 4.58.

Example 89

1-((N-Methylamino)methyl-N-(2-(3-nitro-4-hydroxyphenyl)-ethyl))-6-methoxy tetralin hydrochloride

Using the procedures described in Examples 1-5 but replacing 2-thiopheneacetic acid with 4-acetoxy-3-nitrophenylacetic acid gave the desired product. Anal. calcd. for $C_{21}H_{30}Cl_2N_2O_2 \cdot 1/2 H_2O$: C, 59.71; H, 7.40; N, 6.63. Found: C, 59.59; H, 7.48; N, 6.51.

Example 90

1-((N-Methylamino)methyl-N-(2-(3-amino-4-hydroxyphenyl)-ethyl))-6-methoxy tetralin dihydrochloride

The product from Example 89 was catalytically reduced as in Example 66 but replacing 5% Pd/C with 20% Pd/C and gave the desired compound, m.p. 188-90°C. Anal. calcd. for $C_{21}H_{30}Cl_2N_2O_2 \cdot 1/2 H_2O$: C, 59.71; H, 7.40; N, 6.63. Found: C, 59.59; H, 7.48; N, 6.51.

Example 91

6-Methoxy-1,2,3,4-tetrahydro-1-naphthylene carboxylic acid

A mixture of 1-cyano-6-methoxy-1,2,3,4-tetrahydronaphthalene (18.7g; 0.1 mol), 45% aq. KOH solution (220 ml) and ethylene glycol (180 ml) was refluxed for 6h. The reaction mixture was cooled to 0°C and acidified with cold concentrated hydrochloric acid. The acidic solution was extracted with methylene chloride. The organic layer was washed with brine, separated dried ($MgSO_4$), filtered, and evaporated to afford ca. 20g of an oily residue. Crystallization with

ether/hexane afforded ca. 17.1g (83%) of a white crystalline solid, m.p. 81-82°C.

Example 92

N-Methoxy-N-methyl-6-methoxy-1,2,3,4-tetrahydro-1-naphthylene carboxamide

The product of Example 91 (15g) was dissolved in benzene (100ml) and oxalyl chloride (15ml) and refluxed 1 hr under N_2. The solvent was evaporated and the residue azeotroped with benzene (2 x 40ml). The resulting acid chloride (18.4g), and N,O-dimethylhydroxyl amine hydrochloride was dissolved in ethanol-free chloroform (200ml) and the solution cooled to O°C, then pyridine (13.4ml) was slowly added. The mixture was then stirred at room temperature for 1 h then evaporated to dryness. The residue was partitioned between brine and a 1:1 mixture of Et_2O and CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated affording the desired product as an oil (98% yield).

Example 93

1-(1,2,3,4-Tetrahydro-6-methoxy-1-naphthyl)ethan-1-one

The product from example 92 (4.98g) was dissolved in dry THF (100ml) cooled to O°C, then a solution of methylmagnesium Grignard (20ml of a 2.9M ether solution) was added under N_2. The reaction was stirred at O°C for 1 1/2 hr then diluted with ether (100ml) and poured onto a saturated solution of NH_4Cl. Methylene chloride was added (100ml) and the organic layer separated, washed with brine, dried ($MgSO_4$), filtered and evaporated affording a viscous oil (95% yield).

Example 94

2-(1,2,3,4-Tetrahydro-6-methoxy-1-naphthyl)pyrrolidine

The product from Example 92 (2.49g) was dissolved in dry THF (50ml) and cooled to 0°C. Then, an excess (3-4 equiv.) of 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-propyl magnesium bromide was added and the reaction stirred at 0°C warming to room temperature overnight. The reaction was cooled to 0°C then 10% HCl in EtOH was slowly added, followed by stirring for 3 h at room temperature. The solvent was evaporated and the residue dissolved in methanol. The mixture was cooled to 0°C, then treated with an excess of $NaBH_4$ and the mixture stirred at room temperature for 3 h. The solvent was stripped in vacuo and the residue partitioned between ether and H_2O. The acidic aqueous layer was made basic then extracted with methylene chloride. The organic extract was dried ($MgSO_4$), filtered and evaporated in vacuo and the product purified by column chromatography on silica gel eluting with 1:6 EtOH/CH_2Cl_2 containing NH_4OH affording 1.2 g of desired product.

Example 95

N-(2-(2-Furyl)ethyl)-2-(1,2,3,4-tetrahydro-6-methoxy-1-naphthyl)pyrrolidine difumarate

The product from Example 94 was reacted as described in Examples 18 and 19 but replacing 2-thiopheneacetic acid with 2-furylacetic acid and gave the desired product, m.p. 110-111°C. Anal. calcd. for $C_{29}H_{37}NO_{10}$: C, 62.47; H, 6.33; N, 2.51. Found: C,62.90; H, 6.39; N, 2.55.

Example 96

N-(2-(2-Thienyl)ethyl)-2-(1,2,3,4-tetrahydro-6-methoxy-1-naphthyl)pyrrolidine methanesulfonate

The product from Example 94 was reacted as described in Examples 18 and 19 and afforded the desired product.

Example 97

N-(2-(m-Fluorophenyl)ethyl)-2-(1,2,3,4-tetrahydro-6-methoxy-1-naphthyl) pyrrolidine methanesulfonate

Using the product from Example 94 and the procedures of Examples 18 and 19, but replacing 2-thienylacetic acid with m-fluorophenylacetic acid gave the desired product.

Example 98

1-(6-Methoxy-1-2,3,4-tetrahydro-1-naphthyl)-N-ethyl-1-amino ethane

The product of Example 93(2g) was dissolved in anhydrous MeOH (20ml) and $EtNH_2$ (3ml) and the pH adjusted to ca. 8 with methanolic HCl. Sodium cyanoborohydride (500mg) was added and an additional 2ml methanolic HCl dropwise. The reaction was stirred under N_2 for 48h then 6N HCl added to pH<2. The methanol was removed under vacuum and the aqueous layer extracted with CH_2Cl_2 (2 x 100 ml). The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and evaporated giving 0.18g of an oil. The neutral CH_2Cl_2 extract was dried ($MgSO_4$), filtered and evaporated then partitioned between 2N HCl and a mixture of ether/hexane. The organic layer was separated and discarded. The acidic layer was basified and extracted with CH_2Cl_2. The organic layer was separated, dried

($MgSO_4$), filtered and evaporated giving an additional 1.12g of product.

Example 99

1-(6-Methoxy-1,2,3,4-tetrahydro-1-naphthyl)-N-methyl-1-amino ethane

Using the procedure described in Example 98 but replacing $EtNH_2$ with methylamine afforded the desired product in 59% yield.

Example 100

N-(2-Phenylethyl)-1-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)-N-methyl-1-amino ethane hydrochloride

Using the procedures described in Examples 4 and 5 but replacing the 2-thiopheneacetic acid with phenylacetic acid and the product from Example 99 gave the desired compound, m.p. 159-160°C. Anal. calcd. for $C_{22}H_{30}ClNO$: C, 73.23; H, 8.32; N. 3.88. Found: C, 73.28; H, 8.28; N. 3.86.

Example 101

N-(2-(Phenyl)ethyl)-1-(6-hydroxy-1,2,3,4-tetrahydro-1-naphthyl)-N-methyl-1-amino ethane hydrobromide

Using the product from Example 100 and the procedure of Example 9 gave the desired product, m.p. 88-90°C. Anal. calcd. for $C_{21}H_{28}BrNO$: C, 64.62; H, 7.18; N, 3.59. Found: C, 64.50; H, 7.14; N, 3.54..

Example 102

N-(2-(2-Furyl)ethyl)-1-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)-N-methyl-1-amino ethane methanesulfonate

Using the product from Example 99 and the procedures described in Examples 18 and 19 but replacing

2-thiopheneacetic acid with 2-furylacetic acid gave the desired product, $(M+H)^+$314.

Example 103

N-(2-(2-Thienyl)ethyl)-1-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)-N-methyl-1-amino ethane hydrochloride

Using the product from Example 99 and the procedures described in Examples 4 and 5 gave the desired product, m.p. 160-61°C. Anal. calcd. for $C_{20}H_{28}ClNOS$: C, 65.66; H, 7.66; N, 3.83. Found: C, 65.82; H, 7.74; N, 3.82.

Example 104

N-(2-(2-Furyl)ethyl)-1-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)-N-ethyl-1-amino ethane hydrochloride

Using the compound from Example 98 and the procedures described in Examples 18 and 19 but replacing 2-thiopheneacetic acid with 2-furylacetic acid gave the desired product, $(M+H)^+$328. ^1H NMR ($CDCl_3$): 0.85(3H,d, J=8.0 Hz), 1.04 (3H, t, J=8.0 Hz), 1.32-1.47 (1H,m), 1.61-1.72 (1H,m), 1.75-1.88 (1H,m), 2.26-2.43 (2H,m), 2.5-2.92 (9H,m), 3.75 (3H,s), 6.1 (1H,dd,J=3.0, 0.6 Hz), 6.28 (1H,dd,J=3.0, 1.5 Hz), 6.61 (1H,d,J=3.0 Hz), 6.63 (1H,dd,J=9.0, 3.0 Hz), 7.0 (1H,d,J=8.0 Hz), 7.3 (1H,dd,J=1.5, 0.6 Hz).

Example 105

1-(1,2,3,4-Tetrahydro-6-methoxy-1-naphthyl)propan-1-one

Using the product of Example 92 and the procedure of Example 93 but replacing methyl magnesium bromide with ethyl magnesium bromide gave the desired product.

Example 106

1-(6-Methoxy-1,2,3,4-tetrahydro-1-naphthyl)-N-methyl-1-amino propane

Using the product of Example 105 with the procedure described in Example 98 but replacing the ethylamine with methylamine gave the desired product.

Example 107

N-(2-(2-Furyl)ethyl)-1-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)-N-methyl-1-amino propane hydrochloride

Using the product from Example 106 and following the procedures described in Examples 18 and 19 but replacing 2-thiopheneacetic acid with 2-furylacetic acid gave the desired product. ^{1}H NMR ($CDCl_3$): 0.84-1.0 (5H,m); 1.4-1.9 (3H,m); 2.38 (3H,s); 2.5-2.95 (9H,m); 3.65 (3H,s); 6.1 (1H,dd,J=3.0, 0.6 Hz); 6.29 (1H,dd,J=3.0, 1.5 Hz); 6.59 (1H, d,J=3.0 Hz); 6.63 (1H,dd,J=9.0, 3.0 Hz); 6.90 (1H,d,J=9.0); 7.28 (1H,dd,J=1.5, 0.6 Hz).

Example 108

N-(2-(m-Fluorophenyl)ethyl)-1-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)-N-methyl-1-amino propane hydrochloride

Using the product of Example 106 and the procedures described in Examples 4 and 5 but replacing 2-thiopheneacetic acid with m-fluorophenylacetic acid gave the desired product.

Example 109

N-(2-(m-Fluorophenyl)ethyl)-1-(6-hydroxy-1,2,3,4-tetrahydro-1-naphthyl)-N-methyl-1-amino propane hydrobromide

Using the product of Example 108 with the procedure of Example 9 gave the desired product.

Example 110

N-(2-(m-Fluorophenyl)ethyl)-2-(1,2,3,4-tetrahydro-1-naphthyl-6-hydroxy) pyrrolidine hydrobromide

Using the product from Example 97 and the procedure of Example 9 gave the desired product.

Example 111

1-(N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-5-hydroxy tetralin hydrochloride

1-(N-methylamino)methyl-5-trimethylsilyoxy tetralin was reacted as in Example 18 and gave the desired amide. This amide was then treated as in Example 5 and afforded the desired compound, m.p. 202-3°C (free base).

Example 112

6-Acetamido-3,4-dihydronaphthylene-1-carbonitrile

Using the procedure of Example 1, but replacing 6-methoxy-1-tetralone with 6-acetamido-1-tetralone gave the desired product.

Example 113

6-Amino-(1,2,3,4-tetrahydro-1-naphthylene) carboxylic acid

The product from Example 112 was reduced with $NaBH_4$ in MeOH and DME then hydrolyzed to the

carboxylic acid as described in Example 92.

Example 114

1-((N-Methylaminomethyl-N-(2-phenylethyl))-6-amino tetralin dihydrochloride

Replacing 2-thiopheneacetic acid with the product from Example 113 and using the procedure of Example 18 with N-methylphenethyl amine gave the desired amide. This amide was reduced as in Example 19 and gave the desired product, m.p. 255-56°C. Anal. calcd. for $C_{20}H_{28}Cl_2N_2$: C, 72.59; H, 8.22; N. 8.46. Found: C, 72.42; H, 8.41; H, 8.39.

Example 115

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-5-iodo-6-hydroxy tetralin hydrochloride

The product from Example 7 (free base) was iodinated with silver trifluoroacetate in CH_2Cl_2 at 0°C, and afforded the desired compound.

Example 116

1-((N-Methylamino)methyl-N-(2-phenylethyl))-5-iodo-6-hydroxy tetralin hydrochloride

The product from Example 11 (free base) was iodinated with chloramine-T and sodium iodide then treated with methanolic HCl to give the product, m.p. 112-114°C.

Example 117

1-((N-Methylamino)methyl-N-(2-phenylethyl))-5-iodo-6-amino tetralin dihydrochloride

The product from Example 114 was reacted as described in the procedure of Example 116 and afforded the desired product.

Example 118

1-((N-Methylamino)methyl-N-(3-(2-furyl)propyl))-6-methoxy tetralin hydrochloride

The product from Example 3 was reacted with 2-furylpropionic acid using the procedure of Example 18. The resulting amide was reduced as described in Example 19 and afforded the desired compound, m.p. 140-41°C. Anal. calcd. for $C_{20}H_{28}ClNO_2$: C, 66.33; H, 7.21; N, 4.55. Found: C, 66.27; H, 7.19; N, 4.53.

Example 119

1-((N-Methylamino)methyl-N-(2-(m-methylphenyl)-ethyl))-5-methoxy indane hydrochloride

Using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with 5-methoxy-1-indanone and replacing 2-thiopheneacetic acid with m-methylphenyl acetic acid gave the desired compound, m.p. 183-84°C. Anal. calcd. for $C_{21}H_{28}ClNO.H_2O$: C, 69.31; H, 8.31; N, 3.85. Found: C, 69.44; H, 7.93; N, 3.90.

Example 120

6-Methoxy-1-(3-phenylpyrrolidino-1-carbonyl) tetralin

Using 3-phenylpyrrolidine and the procedure described in Example 4 but replacing 2-thiopheneacetic acid with the product of example 91 gave the desired amide.

Example 121

6-Methoxy-1-(3-phenylpyrrolidino-1-methyl) tetralin hydrochloride

Reduction of the product of Example 120 using the procedure described in Example 17 gave the desired compound, m.p. 228-232°C. Anal. calcd. for $C_{22}H_{28}ClNO$: C, 73.83; H, 7.89; N, 3.91. Found: C, 73.68; H, 7.86; N, 3.91.

Example 122

2-(2-Thienylmethyl)pyrrolidine

Using the procedure of Example 92 but replacing the product of Example 91 with 2-thiopheneacetic acid gave a 90% yield of the desired carboxamide. This carboxamide was reacted as described in Example 94 and gave the desired product in 43% yield.

Example 123

6-Methoxy-1-(2-(2-thienylmethyl)pyrrolidino-1-methyl) tetralin hydrochloride

The product of Example 122 was reacted as described in Example 4 but replacing 2-thiopheneacetic acid with the product of Example 91 gave the desired amide. This was reduced as described in Example 17 and afforded a foam, m.p. 85-89°C. Anal. calcd. for $C_{21}H_{28}ClNOS.1/2\ H_2O$: C, 65.18; H, 7.55; N. 3.62. Found: C, 65.06; H, 7.21; N, 3.82.

Example 124

5-Methoxy-3-phenyl-1-tetralone

o-Anisaldehyde (20.5g) was treated with 1,3-propanedithiol (24 ml) in the presence of BF_3

etherate (4 ml) and CH_2Cl_2 (300 ml). This dithiane derivative (4.7g) was reacted with n-BuLi (2.5 M hexane solution) (7.3 ml), methyl cinnamate (3.4g) and 1,3-dimethyl-2-imidazolidone (4.6 ml) affording the desired product $(M+H)^+$389. Desulfurization was accomplished with Raney Nickel and EtOH, followed by hydrolysis to the desired carboxylic acid. Cyclization to the desired 5-methoxy-3-phenyl-1-tetralone was accomplished by heating with polyphosphoric acid, $(M+H)^+$253.

Example 125

1-(N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-3-phenyl-5-methoxy tetralin hydrochloride

The product from Example 124 was reacted as described in Examples 1-5 and gave the desired product, $(M+H)^+$392.

Example 126

6-Methoxy-3-phenyl-1-tetralone

Using the procedure described in Example 124 but replacing o-anisaldehyde with m-anisaldehyde afforded the desired product, $(M+H)^+$253.

Example 127

1-(N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-3-phenyl-6-methoxy tetralin hydrochloride

The product from Example 126 was treated as described in Examples 1-5 and afforded the desired product, m.p. 155-160°C. Anal. calcd. for $C_{25}H_{30}NOS$: C, 70.15; H, 7.06; N. 3.27. Found: C, 70.42; H, 7.19; N, 3.24.

Example 128

1-((N-Methylamino)methyl-N-(2-(2-furyl)ethyl))-6-methoxy-7-methyl tetralin hydrochloride

Using the procedures described in Examples 1-3 and Examples 18-19 but replacing 6-methoxy-1-tetralone with the product of Example 38 and replacing 2-thiopheneacetic acid with 2-furylacetic acid gave the desired compound, m.p. 188-89C. Anal. calcd. for $C_{20}H_{28}ClNO_2$: C, 68.65; H, 8.07; N, 4.00. Found: C, 68.59; H, 8.20; N, 3.95.

Example 129

1-((N-Methylamino)methyl-N-(2-(2-thieny)ethyl))-5-chloro tetralin hydrochloride

Using the procedures described in Examples 46-49 but replacing 6-chloro-1-tetralone with 5-chloro-1-tetralone afforded the desired product, m.p. 216-217°C. Anal. calcd. for $C_{18}H_{23}Cl_2NS$: C, 60.67; H, 6.18; N, 3.93. Found: C, 60.67; H, 5.57; N, 3.95.

Example 130

6-Methoxy-3-methyl-1-tetralone

The compound was prepared as described in Example 124 replacing methyl cinnamate with ethyl crotonate affording the desired product, $(M+H)^+$191.

Example 131

1-((N-Methylamino)methyl-N-(2-(2-thienyl)ethyl))-3-methyl-6-methoxy tetralin hydrochloride

Using the procedures described in Examples 1-5 but replacing 6-methoxy-1-tetralone with the product of Example 130 gave the desired compound, $(M+H)^+$330.

Example 132

Dimethyl (2-thienyl)methylidene malonate

A solution of 2-thiophene carboxaldehyde (20.0g), dimethyl malonate (22.1 ml), acetic acid (2.0 ml) and piperidine (0.7 ml) in 130 ml of benzene was heated at reflux under azeotropic conditions. After 4 hours the reaction mixture was cooled to room temperature, diluted with Et_2O (100 ml), washed with 5% HCl (50 ml), brine (50 ml), sat. $NaHCO_3$ (50 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. Distillation of the resulting amber oil under reduced pressure afforded 39 g of the desired compound which crystallized upon standing, m.p. 44-46°C.

Example 133

3-Cyano-3-(2-thienyl) propionic acid

To a mechanically stirred solution of 12.4 g of Example 132 in 135 ml of abs. EtOH was added in one portion a solution of KCN (3.9 g) in 7.0 ml of water, and the mixture heated to 70°C. After 20 hr at 70°C, the reaction mixture was cooled to 15°C, filtered, and concentrated in vacuo. The residue was taken up into Et_2O (150 ml) and 10% aq. KOH (100 ml). The layers were separated and the aqueous phase reextracted with Et_2O (100 ml).

The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated to afford an amber liquid. Bulb to bulb distillation under reduced pressure afforded 7.89 g of a pale yellow liquid which was carried on to the next reaction without further purification.

Example 134

4-(2-Thienyl)-2-pyrrolidinone

To a suspension of 1.23 g of cobalt boride and 2.0 g of the product of Example 133 in 60 ml of absolute methanol was added 2.50 g of borane tert-butyl amine complex, and the reaction was heated to reflux. After 6 h at reflux, the reaction was cooled to room temperature, filtered and concentrated. The residue was taken up unto EtOAc (70 ml) and 5% aqueous HCl (25 ml). The phases were separated and the aqueous phase reextracted with EtOAc (50 ml). The extracts were combined, dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue on silica gel (elution with EtOAc) afforded 0.775 g of product as a white, crystalline material, m.p. 75.0-76.5°C. Anal. calcd. for C_8H_9NOS: C, 57.46; H, 5.42; N, 8.38. Found: C, 57.64; H, 5.58; N, 8.47.

Example 135

3-(2-Thienyl)pyrrolidine

To a suspension of $LiAlH_4$ (0.46g) in THF (25 ml) was added the product of Example 134 (1.0 g) in THF (30 ml). After the addition was complete the reaction was heated at reflux for 4 hrs.

The reaction was cooled to 0°C and quenched by the dropwise addition of water (0.46 ml), 15% aq. KOH (0.46 ml), followed by another 1.4 ml of water. After 30 min., the reaction was filtered and concentrated. The residue was taken up into EtOAc (60 ml), washed thoroughly with 5% aq. HCl (2 x 30 ml). The aqueous phases were combined, basified with 15% aq. KOH to pH 10 and extracted with EtOAc (2 x 50 ml). The organic

extracts were combined, dried ($MgSO_4$), filtered and concentrated. Bulb-to-bulb distillation under reduced pressure afforded the desired product, $(M+H)^+$154.

Example 136

6-Methoxy-1-(3-(2-thienyl)pyrrolidino-1-methyl) tetralin hydrochloride

Using the products of Examples 91 and 135 and the procedures described in Examples 4 and 17, the desired compound was afforded, 114-117°C dec. Anal. calcd. for $C_{20}H_{26}ClNOS$: C, 66.00; H, 7.20; N, 3.85. Found: C, 65.68; H, 7.14; N, 3.79.

Example 137

N-(2-(2-furyl)ethyl)-2-(1,2,3,4-tetrahydro-6-hydroxy-1-naphthyl) pyrrolidine hydrobromide

The product of Example 95 was reacted as described in Example 9 and gave the desired compound.

Example 138

N-(2-(2-Furyl)ethyl)-2-(1,2,3,4-tetrahydro-6-methoxy-3-methyl-1-naphthyl) pyrrolidine hydrochloride

The product from Example 133 was reacted as described in Example 13 and then Examples 91 and 92. This product was treated as in Example 94 and then Examples 18 and 19, affording the desired compound.

Example 139

N-(2-(2-Furyl)ethyl)-2-(1,2,3,4-tetrahydro-6-hydroxy-3-methyl-1-naphthyl) pyrrolidine hydrobromide

The product of Example 138 was reacted as in Example 9 giving the compound.

Example 140

N-(2-(2-Furyl)ethyl)-2-(1,2,3,4-tetrahydro-6-methoxy-3-phenyl-1-naphthyl) pyrrolidine hydrochloride

The product of Example 126 was reacted as described in Example 13 and then Examples 91 and 92. This product was used as described in Example 94, followed by Examples 18 and 19, giving the desired compound.

Example 141

1-((N-methylamino)methyl-N-(2-(2-furyl)ethyl))-6-methoxy-7-fluoro tetralin methanesulfonate

Using the procedures described in Example 1 but replacing 6-methoxy-1-tetralone and ZnI_2 with 6-methoxy-7-fluoro tetralone and LiCN afforded the 1-cyano derivative. Catalytic reduction with Pd/C at 4 atm. gave the corresponding 1-aminomehtyl tetrali derivative in 97% yield. Utilizing this product and the procedures in examples 16-19 gave the desired product, m.p. 115-116°C. Anal. calcd. for $C_{19}H_{24}NO_2F.CH_3SO_3H$: C, 58.09; H,6.82; N, 3.39. Found: C, 57.86; H, 6.84; N, 3.43.

Example 142

1,2,3,4-Tetrahydro-5,6-methylenedioxy-1-naphthylene carboxylic acid

To a solution of 1-cyano-3,4-dihydro-5,6-methylenedioxynaphthylene (5.0 g) in ethanol (80 ml) was added in small portions sodium borohydride (1.44 g). After the addition was complete the reaction was heated to reflux. After 2 hours, the reaction was cooled and

concentrated. The residue was taken up into 1 N HCl and CH_2Cl_2 and the layers separated. The organic phase was washed with water, brine, dried over $MgSO_4$, filtered and concentrated. The resulting material was dissolved into ethylene glycol(41 ml) treated with 45% KOH (30 ml) and heated to reflux. After 3 hours the reaction was cooled with an ice bath, diluted with ice/water and acidified with concentrated HCl, upon which a white precipitate formed. The product was extracted with ethyl acetate (3 x 75 ml), washed with brine, dried over $MgSO_4$, filtered and concentrated to afford the desired product, m.p. 165-167°C.

Example 143

5,6-Methylenedioxy-1-(3-phenylpyrrolidino-1-methyl) tetralin methanesulfonate

Using 3-phenylpyrrolidine and the procedures described in Examples 4 and 5 but replacing 2-thiopheneacetic acid with Example 142 afforded the desired compound, m.p. 123-124°C. Anal. calcd. for $C_{22}H_{25}NO_2 \cdot CH_3SO_3H$: C, 64.01; H, 6.77; N. 3.25. Found: C, 63.97; H. 6.83; N. 3.22.

Example 144

5,6-Methylenedioxy-1-(3-(2-thienyl)pyrrolidino-1-methyl) tetralin methanesulfonate

Using Example 135 and the procedures described in Examples 4 and 5 but replacing 2-thiopheneacetic acid with Example 142 afforded the desired compound, m.p. 150-151°C. Anal. calcd. for $C_{20}H_{23}NO_2S \cdot CH_3SO_3H$: C, 57.64; H, 6.22; N, 3.20. Found: C, 57.17; H, 6.16; N, 3.15.

Example 145

1,2,3,4-Tetrahydro-5-methoxy-1-naphthylene carboxylic acid

Using the procedure described in Example 142 but replacing 1-cyano-3,4-dihydro-5,6-methylenedioxynaphthylene with 1-cyano-3,4-dihydro-5-methoxynaphthylene provided the desired product, m.p. 101-102°C.

Example 146

5-Methoxy-1-(3-(2-thienyl)pyrrolidino-1-methyl) tetralin hydrochloride

Using Example 135 and the procedures described in Examples 4 and 5 but replacing 2-thiopheneacetic acid with Example 145 afforded the desired compound, m.p. >230°C. Anal calcd. for $C_{20}H_{25}NOS.HCl$: C, 66.00; H, 7.20; N, 3.85. Found: C, 65.87; H, 7.19; N, 3.83.

Example 147

6 -Fluoro-1,2,3,4-tetrahydro-1-naphthylene carboxylic acid

Using the procedure described in Example 142 but replacing 1-cyano-3,4-dihydro-5,6-methylenedioxynaphthylene with 1-cyano-6-fluoro-3,4-dihydronaphthylene provided the desired product, m.p. 90-91°C.

Example 148

6-Fluoro-1-(3-phenylpyrrolidino-1-methyl) tetralin methanesulfonate

Using 3-phenylpyrrolidine and the procedures described in Examples 4 and 5 but replacing

2-thiopheneacetic acid with Example 147 afforded the desired compound, m.p. 166-167°C. Anal. calcd. for $C_{21}H_{24}FN.CH_3SO_3H$: C, 65.16; H, 6.96; N, 3.45. Found: C, 64.98; H, 6.93; N, 3.42.

Example 149

6-Fluoro-1-(3-(2-thienyl)pyrrolidino-1-methyl) tetralin methanesulfonate

Using Example 135 and the procedures described in Examples 4 and 5 but replacing 2-thiopheneacetic acid with Example 147 afforded the desired compound, m.p. 136-137°C. Anal. calcd. for $C_{19}H_{24}FN.CH_3SO_3H$: C. 58.37; H, 6.37; N. 3.40. Found: C, 58.22; H, 6.34; N, 3.35.

Example 150

2,3-Dihydro-4-methoxy-1-indene carboxylic acid

Using the procedure described in Example 142 but replacing 1-cyano-3,4-dihydro-5,6-methylenedioxynaphthylene with 1-cyano-2,3-dihydro-5-methoxy-1-indene provided the desired product, m.p. 117-118°C.

Example 151

5-Methoxy-1-(3-(2-thienyl)pyrrolidino-1-methyl) indane hydrochloride

Using Example 135 and the procedures described in Examples 4 and 5 but replacing 2-thiopheneacetic acid with Example 150 provided the desired compound, m.p. 202-204°C dec. Anal. calcd. for $C_{19}H_{23}NOS.HCl$: C, 65.22; H, 6.91; N, 4.00. Found: C, 65.04; H, 6.92; N, 3.93.

Example 152

5-Methoxy-1-(3-phenylpyrrolidino-1-methyl) indane hydrochloride

Using 3-phenylpyrrolidine and the procedures described in Examples 4 and 5 but replacing 2-thiopheneacetic acid with Example 150 provided the desired compound, m.p. 126-130°C dec. Anal. calcd. for $C_{22}H_{25}NO.CH_3SO_3H$: C, 65.48; H, 7.24; N, 3.47. Found: C, 65.44; H, 7.31; N. 3.46.

Example 153

5-Methoxy-1-(3-(m-fluorophenyl)pyrrolidino-1-methyl) indane hydrochloride

Using 3-(m-fluorophenyl)pyrrolidine and the procedures described in Examples 4 and 5 but replacing 2-thiopheneacetic acid with Example 150 provided the desired compound, m.p. 205-207°C dec. Anal. calcd. for $C_{21}H_{24}FNO.HCl$: C, 69.70; H, 6.96; N, 3.87. Found: C, 69.54; H, 7.06; N, 3.83.

Example 154

6-Amino-1,2,3,4-tetrahydro-1-naphthylene carboxylic acid hydrochloride

Using the procedure outlined in Example 1 but replacing 6-methoxy-1-tetralone with 6-acetamido-1-tetralone afforded the desired unsaturated nitrile. A suspension of the above nitrile (24 g) in 260 mL of a 1:1 mixture of ethanol and dimethoxyethyl ether was treated with small portions of sodium borohydride (15 g). After the addition was complete the reaction was heated at reflux for 20 hours. The reaction was cooled to room temperature, quenched by the

dropwise addition of acetone and concentrated. The residue was taken up into saturated NH_4Cl and CH_2Cl_2. The phases were separated and the aqueous phase reextracted with CH_2Cl_2. The organic extracts were combined, dried over magnesium sulfate, filtered and concentrated to provide the desired saturated nitrile.

The above nitrile was taken up into concentrated hydrochloric acid (160 ml) and heated at reflux for 5 hours. The reaction was cooled to 0°C and the resulting precipitate collected and washed with a 10% ethanol/ether solution to provide the desired product.

Example 155

1-((6-amino-1,2,3,4-tetrahydro-1-naphthalenyl)carbonyl)-3-phenylpyrrolidine

A mixture of Example 154 (2.3 g) and thionyl chloride (50 ml) were heated at reflux for 45 minutes. The reaction was concentrated and the residue was co-concentrated with toluene (3 x 50 ml). To a solution of 3-phenylpyrrolidine in CH_2Cl_2 (30 ml) containing triethylamine (4.2 ml) at 0°C, was added dropwise a solution of the above acid chloride in CH_2Cl_2 (30 ml). After 8 hours, the reaction was concentrated to afford a brown oil. The residue was taken up into a mixture of water and ethyl acetate. The layers were separated and the organic phase washed with 1N NaOH, brine, dried over magnesium sulfate, filtered and concentrated. Chromatography (elution with 2% CH_3OH/CH_2Cl_2) on silica gel provided 2.7 g of the desired product.

Example 156

6-Amino-1-(3-phenylpyrrolidino-1-methyl) tetralin dihydrochloride

Using the procedure described in Example 19 but replacing Example 18 with Example 155 yielded the desired compound, m.p. >260°C. Anal. calcd. for $C_{21}H_{26}N_2 \cdot 2HCl$: C, 66.49; H, 7.44; N, 7.38. Found: C, 65.81; H, 7.41; N. 7.21.

Example 157

6-(N-methylamino)-1-(3-phenylpyrrolidino-1-methyl) tetralin dihydrochloride

Using the procedure outlined in Example 3 but replacing Example 2 with Example 155 provided the desired compound, m.p. 231°C. Anal. calcd. for $C_{22}H_{28}N_2 \cdot 2HCl$: C, 67.17; H, 7.69; N, 7.12. Found: C, 66.97; H, 7.88; N,. 7.12.

Example 158

8-fluoro-5,6,methylenedioxy-1-tetralone

To a solution of 8-fluoro-5,6-dimethoxy-1-tetralone (3.0 g) in toluene (30 ml) was added in small portions aluminum chloride (9.0 g). After the addition was complete, the reaction was heated to 80°C and after 30 min. cooled to room temperature. The reaction mixture was poured into concentrated HCl/ice and the product extracted with ethyl acetate. The organic layer was washed with 1 N HCl, brine, dried over $MgSO_4$, filtered and concentrated to afford 2.0 g of product. To a suspension of this material in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone (10

ml) was added 540 mg of sodium hydride in small portions. After 20 min., the reaction was treated with diiodomethane (0.95 ml) and the reaction allowed to stir for 8 hours. The reaction was poured into water (50 ml) and extracted with ethyl acetate (2 x 50 ml). The extracts were combined, washed with water, dried over $MgSO_4$, filtered and concentrated. Chromatography of the residue on silica gel (elution with 25% EtOAc/hexanes) afforded the desired product, m.p. 174-175°C.

Example 159

8-Fluoro-1,2,3,4-tetrahydro-5,6-methylenedioxy-2-naphthylene carboxylic acid

Using the procedure in Example 1, but replacing 6-methoxy-1-tetralone with Example 158 afforded the unsaturated nitrile. This material was subjected to the reaction conditions described in Example 142 to provide the desired material.

Example 160

8-Fluoro-5,6-methylenedioxy-1-(3-phenylpyrrolidino-1-methyl) tetralin hydrochloride

Using 3-phenylpyrrolidine and the procedures described in Example 4 and 5 but replacing 2-thiopheneacetic acid with Example 159 afforded the desired compound.

Example 161

8-Fluoro-5,6-methylenedioxy-1-(3-(m-fluorophenyl) pyrrolidino-1-methyl) tetralin hydrochloride

Using 3-(m-fluorophenyl)pyrrolidine and the procedures described in Example 4 and 5 but replacing

2-thiopheneacetic acid with Example 159 afforded the desired compound.

Example 162

8-Fluoro-5,6-methylenedioxy-1-(3-(2-thienyl)pyrrolidino-1-methyl) tetralin hydrochloride

Using Example 135 and the procedures described in Example 4 and 5 but replacing 2-thiopheneacetic acid with Example 159 afforded the desired compound.

Example 163

5.6-Methylenedioxy-1-(3-(m-fluorophenyl)pyrrolidino-1-methyl) tetralin methanesulfonate

Using 3-(m-fluorophenyl)pyrrolidine and the procedures described in Example 4 and 5 but replacing 2-thiopheneacetic acid with Example 142 afforded the desired compound, m.p. 177-179°C dec. Anal. calcd. for $C_{22}H_{24}FNO_2 \cdot CH_3SO_3H$: C, 61.45; H, 6.28; N, 3.12. Found: C, 61.27; H, 6.32; N, 3.07.

Example 164

1-((N-Ethylamino)methyl-N-(2-(2-thienyl)ethyl))-5,6-methylenedioxy tetralin hydrochloride

The desired compound (m.p. 163-164°C) was prepared using the procedures outlined in examples 1, 2, 15, 4 and 5, but replacing 6-methoxy-1-tetralone with 5,6-methylenedioxy-1-tetralone. Anal. calcd. for $C_{20}H_{25}NO_2S.HCl$: C, 63.23; H. 6.90; N. 3.69. Found: C, 63.15; H, 6.86; N, 3.64.

Example 165

1-((N-Ethylamino)methyl-N-(2-(m-fluorophenethyl)-5,6-methylenedioxy tetralin hydrochloride

The desired compound (m.p. 131.5-132.5°C) was prepared using the procedures in Example 165, but replacing 2-thiopheneacetic acid with m-fluorophenylacetic acid. Anal calcd. for $C_{22}H_{26}FNO_2.HCl$: C, 67.42; H, 6.94; N, 3.57. Found: C, 67.40; H, 6.98; N, 3.51.

Example 166

1-((N-Methylamino)methyl-N-(2-(m-fluorophenethyl))-5,6-methylenedioxy tetralin methanesulfonate

Using the procedures in Example 23, but replacing 2-thiopheneacetic acid with m-fluoroacetic acid provided the desired product upon formation of the methanesulfonate salt, m.p. 144-147°C. Anal. calcd. for $C_{21}H_{24}FNO_2.CH_3SO_3H$: C, 60.39; H, 6.45; N, 3.20. Found: C, 60.39; H. 6.48; N. 3.23.

Example 167

1-((N-Methylamino)methyl-N-(2-(m-fluorophenethyl))-5,6-ethylenedioxy tetralin methanesulfonate

The product was prepared (m.p. 174.175°C) using the procedures in Example 30, but replacing 2-thiopheneacetic acid with m-fluorophenylacetic acid and formation of the methanesulfonate salt. Anal. calcd. for $C_{22}H_{26}FNO_2.CH_3SO_3H$: C, 61.18; H. 6.70; N, 3.10. Found: C, 60.94; H, 6.71; N, 3.09.

Example 168

1-((N-Ethylamino)methyl-N-(2-(2-thienyl)ethyl))-5,6-ethylenedioxy tetralin hydrochloride

Using the procedures outlined in Example 164, but replacing 5,6-methylenedioxy-1-tetralone with 5,6-ethylenedioxy-1-tetralone provided the desired product. Anal. calcd. for $C_{21}H_{27}NO_2S.HCl.1/2H_2O$: C, 62.59; H. 7.25; N. 3.48. Found: C, 62.50; H, 6.95; N, 3.55.

Example 169

1,2,3,4-Tetrahydro-5,6-ethylenedioxy-1-naphthylene carboxylic acid

Using the procedure in Example 142 but replacing 1-cyano-3,4-dihydro-5,6-methylenedioxy-naphthylene with 1-cyano-3,4-dihydro-5,6-ethylene-dioxynaphthylene provided the desired material.

Example 170

5,6-Ethylenedioxy-1-(3-phenylpyrrolidino-1-methyl) tetralin hydrochloride

Using 3-phenylpyrrolidine and the procedures described in Examples 4 and 5 but replacing 2-thiopheneacetic acid with Example 169 afforded the desired compound.

Example 171

5,6-Ethylenedioxy-1-(3-(m-fluorophenyl)pyrrolidino-1-methyl) tetralin hydrochloride

Using 3-(m-fluorophenyl)pyrrolidine and the procedures described in Examples 4 and 5 but replacing 2-thiopheneacetic acid with Example 169 afforded the desired compound.

Example 172

5,6-Ethylenedioxy-1-(3-(2-thienyl)pyrrolidino-1-methyl) tetralin hydrochloride

Using 3-(2-thienyl)pyrrolidine and the procedures described in Examples 4 and 5 but replacing 2-thiopheneacetic acid with Example 169 afforded the desired compound.

The compounds were assessed for alpha-adrenergic receptor subtype selectivity by use of radioligand binding techniques as described previously (DeBernardis et.al. J. Med. Chem. 28, 1398 (1985)). Affinity for the alpha-1-receptor was assessed using rat liver homogenates and the radioligand [^{3}H]-prazosin; whereas for the alpha-2-receptor, rat cerebral cortices and the radioligand [^{3}H]-rauwolscine were utilized. Results obtained from the binding studies are shown in Table 1 for a representative sample of compounds disclosed herein, showing clearly the excellent affinity for the alpha-2-receptor, as well as the high degree of selectivity relative to the alpha-1-adrenoceptor.

Table 1. Radioligand Binding Data at alpha 1- and alpha 2- Adrenoceptors for Representative Compounds

Example #	K_i(nM) alpha-1	K_i(nM) alpha-2	alpha-2 - Selectivity K_i alpha-1/K_i alpha-2
5	580	0.8	725
6b	1180	5.0	236
6d	500	1.5	333
6f	2160	6.5	332
6h	1505	3.5	430
7	565	1.6	353
12	1208	5.0	242
22	695	1.3	535
23	445	1.7	262
26	175	0.6	292
27	525	2.0	263
30	470	4.0	118
34	330	2.6	127
36	655	6.9	95
37	645	3.7	174
41	950	2.9	326
42	1050	6.6	159
43	1400	6.0	233
44	590	5.6	105
49	1125	10.0	113
58	1830	18.0	102
67	1170	6.0	195
68	1175	6.0	196
69	1275	13.0	98
70	525	5.0	105

82	495	4.0	124
83	955	8.0	119
85	260	1.5	173
86	495	3.0	165
87	444	1.6	278
88	315	2.0	158
114	725	5.7	127
115	530	3.0	177
121	95	1.0	95
128	855	8.0	107
129	198	3.6	55
141	880	4.8	183
143	51	1.2	43
144	245	1.2	204
146	170	4.9	35
148	126	6.5	19
149	220	4.9	45
151	177	2.5	71
152	51	4.8	11
153	58	8.6	7
156	125	6.0	21
164	954	3.7	258
165	462	3.5	132
166	603	4.5	134
167	357	4.2	85
168	823	6.6	125
Rauwolscine	392	4.2	93

The compounds of the invention can be administered in any effective pharmaceutically acceptable form to warm blooded animals, e.g., in oral, parenteral or infusable dosage forms, or as a buccal or nasal spray.

Suitable parenteral routes of administration include, for example, intramuscular, intravenous, intraperitoneal or subcutaneous administration of the compounds.

In addition to the active compounds, compositions according to this invention for parenteral injection may comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, suspensions or emulsions. Examples of suitable nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils, such as olive oil, and injectable organic esters such as ethyl oleate. Such compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized, for example, by filtration through a bacteria-retaining filter, or by incorporating sterilizing agents into the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or other sterile injectable medium, immediately before use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

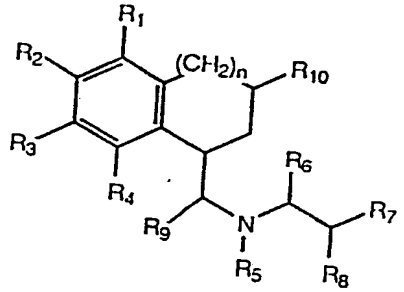
Actual dosage levels of active ingredient in the compositions of the invention may be varied so as to obtain an amount of active ingredient effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, on the route of administration, on the desired duration of treatment and other factors. Generally, dosage levels of about 0.1 to about 200, more preferably about 0.5 to about 150 and most preferably about 1 to about 125 mg of active ingredient per kg of body weight per day are administered orally to a mammalian patient suffering from depression. If desired, the daily dose may be divided into multiple doses for administration, e.g., two to four separate doses per day.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

CLAIMS

What is claimed is:

1. A compound of the formula:



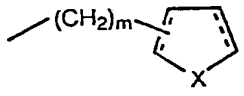
wherein n is 0 or 1;

R_1, R_2, R_3, and R_4 are independently selected from hydrogen, hydroxy, amino, alkylamino, alkylsulfonylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge;

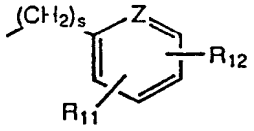
R_5 is loweralkyl;

R_6 and R_8 are hydrogen;

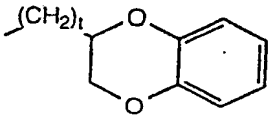
R_7 is



wherein m is 0, 1 or 2 and X is CH_2, O, S or $N-CH_3$; or R_7 is



wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is

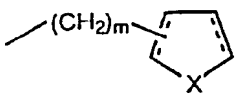


wherein t is 0 or 1;

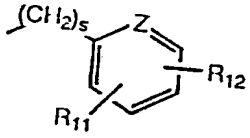
R_9 is hydrogen or loweralkyl; and

R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or

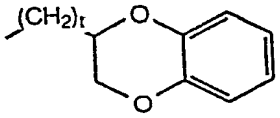
R_5 and R_9 taken together form a pyrrolidine ring and then R_6 and R_8 are hydrogen and R_7 is



wherein m is 0, 1 or 2 and X is CH_2, O, S or $N-CH_3$; or R_7 is



wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is



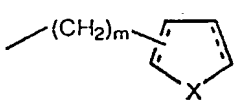
wherein t is 0 or 1; or

R_5 and R_9 taken together form a pyrrolidine ring and then R_6 is hydrogen and R_7 and R_8 taken together form a phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or

R_5 and R_8 taken together form a pyrrolidine ring and then R_9 and R_6 are hydrogen and R_7 is phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents

independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or R_7 and R_9 are hydrogen and R_6 is benzyl, thienylmethyl, furylmethyl or substituted benzyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or a pharmaceutically acceptable salt thereof;

with the proviso that when R_4 is hydrogen; R_1, R_2 and R_3 are independently selected from hydrogen, hydroxy and loweralkoxy, or R_1 and R_2 or R_2 and R_3 taken together form a methylenedioxy bridge; R_{10} is hydrogen; n is 1; R_9 is hydrogen; R_5 is loweralkyl; and R_6 and R_8 are hydrogen, then R_7 is



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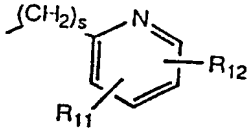
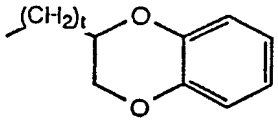


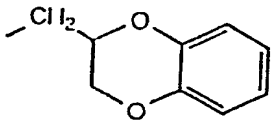
or



wherein R_{11}, R_{12}, m, s and t are as defined previously.

2. A compound of Claim 1 wherein R_1, R_2, R_3 and R_4 are independently selected from hydrogen, halo and loweralkoxy; or R_1 and R_2 or R_2 and R_3 taken together form a methylenedioxy or ethylenedioxy bridge; R_5 is methyl or ethyl or R_5 and R_8 taken

together form a pyrrolidine ring; n is 1; R_7 is thienyl, furyl, (2-thienyl)methyl, (2-furyl)methyl, substituted phenyl or substituted benzyl wherein the phenyl ring is substituted by one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy, or R_7 is

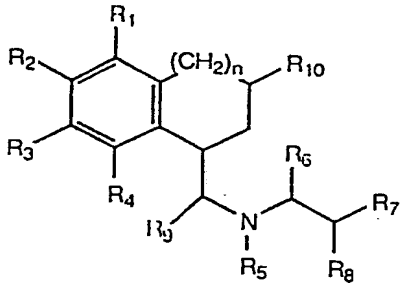


;

R_9 is hydrogen; and R_{10} is hydrogen or methyl.

3. A compound of Claim 1 wherein R_5 and R_9 taken together form a pyrrolidine ring or R_5 and R_8 taken together form a pyrrolidine ring.

4. A pharmaceutical composition for selectively inhibiting alpha-2-adrenergic receptors comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the formula:



wherein n is 0 or 1;

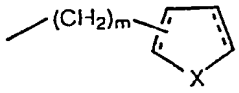
R_1, R_2, R_3, and R_4 are independently selected

from hydrogen, hydroxy, amino, alkylamino, alkylsulfonylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge;

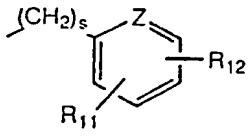
R_5 is loweralkyl;

R_6 and R_8 are hydrogen;

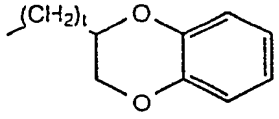
R_7 is



wherein m is 0, 1 or 2 and X is CH_2, O, S or $N-CH_3$; or R_7 is



wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is

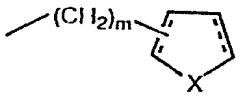


wherein t is 0 or 1;

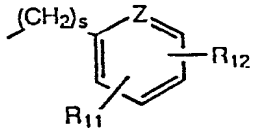
R_9 is hydrogen or loweralkyl; and

R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or

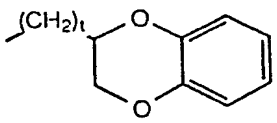
R_5 and R_9 taken together form a pyrrolidine ring and then R_6 and R_8 are hydrogen and R_7 is



wherein m is 0, 1 or 2 and X is CH_2, O, S or $N-CH_3$; or R_7 is



wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is

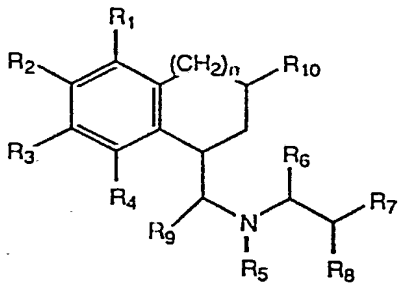


wherein t is 0 or 1; or

R_5 and R_9 taken together form a pyrrolidine ring and then R_6 is hydrogen and R_7 and R_8 taken together form a phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or

R_5 and R_8 taken together form a pyrrolidine ring and then R_9 and R_6 are hydrogen and R_7 is phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or R_7 and R_9 are hydrogen and R_6 is benzyl, thienylmethyl, furylmethyl or substituted benzyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition for treating depression comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the formula:



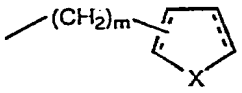
wherein n is 0 or 1;

R_1, R_2, R_3, and R_4 are independently selected from hydrogen, hydroxy, amino, alkylamino, alkylsulfonylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge;

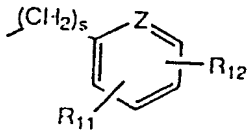
R_5 is loweralkyl;

R_6 and R_8 are hydrogen;

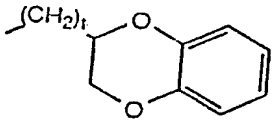
R_7 is



wherein m is 0, 1 or 2 and X is CH_2, O, S or $N-CH_3$; or R_7 is



wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is

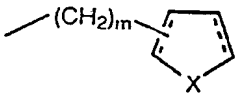


wherein t is 0 or 1;

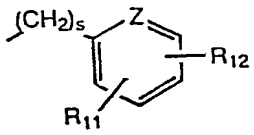
R_9 is hydrogen or loweralkyl; and

R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or

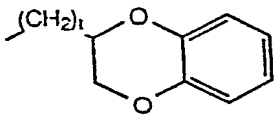
R_5 and R_9 taken together form a pyrrolidine ring and then R_6 and R_8 are hydrogen and R_7 is



wherein m is 0, 1 or 2 and X is CH_2, O, S or N-CH_3; or R_7 is



wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is



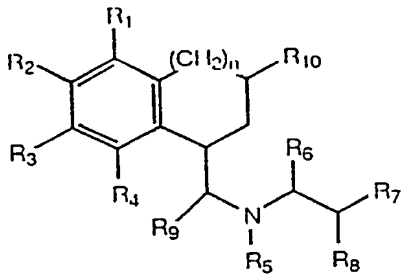
wherein t is 0 or 1; or

R_5 and R_9 taken together form a pyrrolidine ring and then R_6 is hydrogen and R_7 and R_8 taken together form a phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or

R_5 and R_8 taken together form a pyrrolidine ring and then R_9 and R_6 are hydrogen and R_7 is phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents

independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or R_7 and R_9 arehydrogen and R_6 is benzyl, thienylmethyl, furylmethyl or substituted benzyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or a pharmaceutically acceptable salt thereof.

6. A method for selectively inhibiting alpha-2-adrenergic receptors comprising administering to a patient in need, a therapeutically effective amount of a compound of the formula:



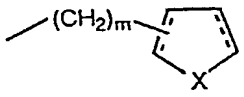
wherein n is 0 or 1;

R_1, R_2, R_3, and R_4 are independently selected from hydrogen, hydroxy, amino, alkylamino, alkylsulfonylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge;

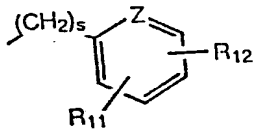
R_5 is loweralkyl;

R_6 and R_8 are hydrogen;

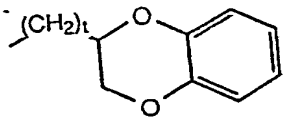
R_7 is



wherein m is 0, 1 or 2 and X is CH_2, O, S or $N-CH_3$; or R_7 is



wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is



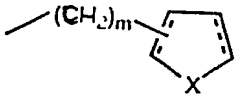
wherein t is 0 or 1;

R_9 is hydrogen or loweralkyl; and

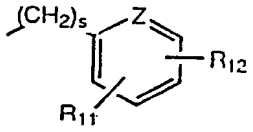
R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with one, two or three substituents independently selected

from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or

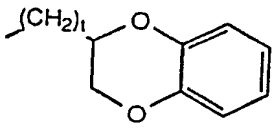
R_5 and R_9 taken together form a pyrrolidine ring and then R_6 and R_8 are hydrogen and R_7 is



wherein m is 0, 1 or 2 and X is CH_2, O, S or $N-CH_3$; or R_7 is



wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is



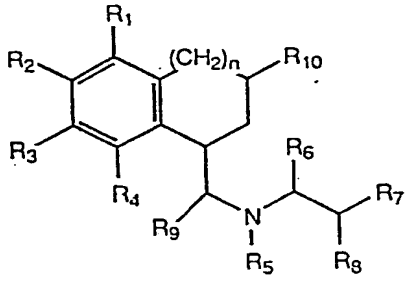
wherein t is 0 or 1; or

R_5 and R_9 taken together form a pyrrolidine ring and

then R_6 is hydrogen and R_7 and R_8 taken together form a phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or

R_5 and R_8 taken together form a pyrrolidine ring and then R_9 and R_6 are hydrogen and R_7 is phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or R_7 and R_9 are hydrogen and R_6 is benzyl, thienylmethyl, furylmethyl or substituted benzyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or a pharmaceutically acceptable salt thereof.

7. A method for treating depression comprising administering to a patient in need, a therapeutically effective amount of a compound of the formula:



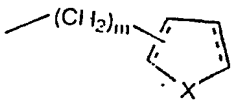
wherein n is 0 or 1;

R_1, R_2, R_3, and R_4 are independently selected from hydrogen, hydroxy, amino, alkylamino, alkylsulfonylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge;

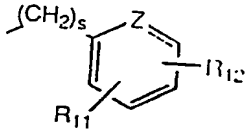
R_5 is loweralkyl;

R_6 and R_8 are hydrogen;

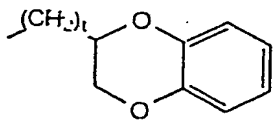
R_7 is



wherein m is 0, 1 or 2 and X is CH_2, O, S or $N-CH_3$; or R_7 is



wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is

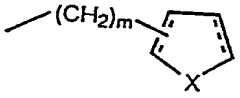


wherein t is 0 or 1;

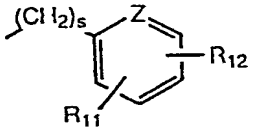
R_9 is hydrogen or loweralkyl; and

R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or

R_5 and R_9 taken together form a pyrrolidine ring and then R_6 and R_8 are hydrogen and R_7 is

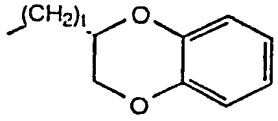


wherein m is 0, 1 or 2 and X is CH_2, O, S or $N-CH_3$; or R_7 is



wherein s is 0, 1, or 2; Z is C or N; and R_{11} and

R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is

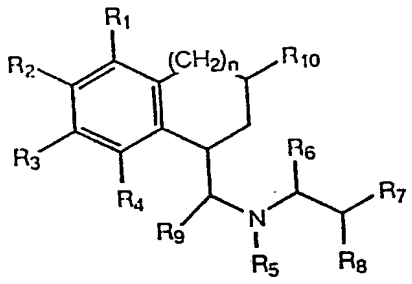


wherein t is 0 or 1; or

R_5 and R_9 taken together form a pyrrolidine ring and then R_6 is hydrogen and R_7 and R_8 taken together form a phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or

R_5 and R_8 taken together form a pyrrolidine ring and then R_9 and R_6 are hydrogen and R_7 is phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or R_7 and R_9 are hydrogen and R_6 is benzyl, thienylmethyl, furylmethyl or substituted benzyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or a pharmaceutically acceptable salt thereof.

8. A process for the preparation of a compound of the formula:



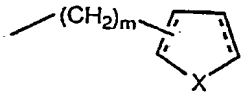
wherein n is 0 or 1;

R_1, R_2, R_3, and R_4 are independently selected from hydrogen, hydroxy, amino, alkylamino, alkylsulfonylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge;

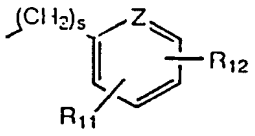
R_5 is loweralkyl;

R_6 and R_8 are hydrogen;

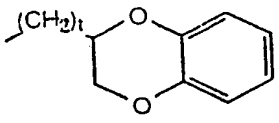
R_7 is



wherein m is 0, 1 or 2 and X is CH_2, O, S or N-CH_3; or R_7 is



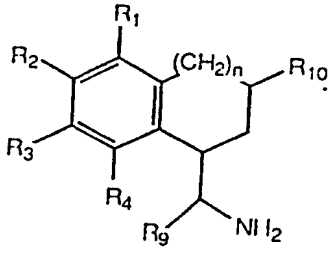
wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is



wherein t is 0 or 1;

R_9 is hydrogen or loweralkyl; and

R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; comprising alkylating a compound of the formula

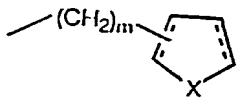


wherein n is 0 or 1;

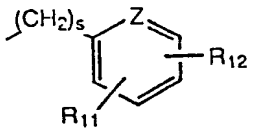
R_1, R_2, R_3, and R_4 are independently selected from hydrogen, hydroxy, amino, alkylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge; and

R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy.

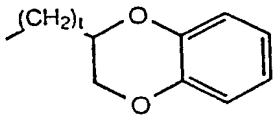
9. The process of Claim 8 wherein the alkylation process to introduce R_5 comprises reaction with R_5COOH or an acid halide, ester or activated ester derivative thereof, wherein R_5 is hydrogen, methyl or ethyl, followed by reduction of the resulting amide; and wherein the alkylation process to introduce $-CH_2CH_2R_7$ comprises reaction with R_7CH_2COOH or an acid halide, ester or activated ester derivative thereof, wherein R_7 is



wherein m is 0, 1 or 2 and X is CH_2, O, S or $N-CH_3$; or R_7 is

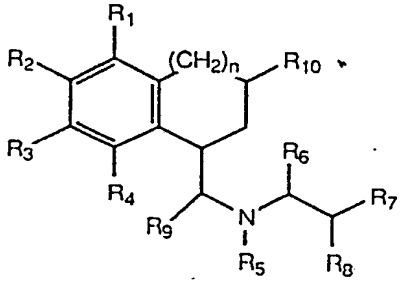


wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is



wherein t is 0 or 1; followed by reduction of the resulting amide.

10. A process for the preparation of a compound of the formula:



wherein n is 0 or 1;

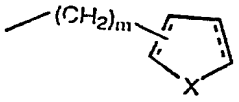
R_1, R_2, R_3, and R_4 are independently selected from hydrogen, hydroxy, amino, alkylamino, alkylsulfonylamino, loweralkyl, loweralkoxy, halo, and

thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge;

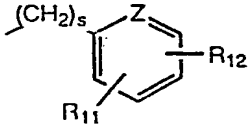
R_5 is loweralkyl;

R_6 and R_8 are hydrogen;

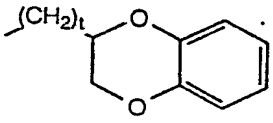
R_7 is



wherein m is 0, 1 or 2 and X is CH_2, O, S or $N-CH_3$; or R_7 is



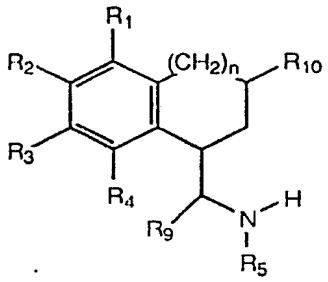
wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is



wherein t is 0 or 1;

R_9 is loweralkyl; and

R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; comprising alkylating a compound of the formula



wherein n is 0 or 1;

R_1, R_2, R_3, and R_4 are independently selected from hydrogen, hydroxy, amino, alkylamino, alkylsulfonylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge;

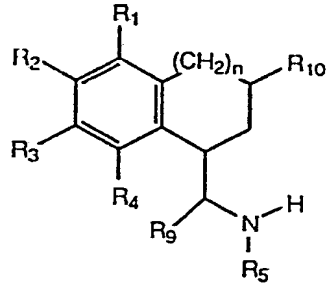
R_5 is loweralkyl;

R_9 is loweralkyl; and

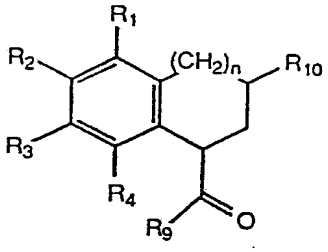
R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with

one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy.

11. The process of Claim 10 wherein the compound of the formula



is prepared by amination of a compound of the formula



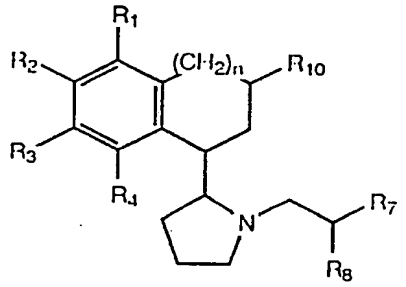
wherein n is 0 or 1;

R_1, R_2, R_3, and R_4 are independently selected from hydrogen, hydroxy, amino, alkylamino, alkylsulfonylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge;

R_9 is loweralkyl; and

R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy.

12. A process for the preparation of a compound of the formula:

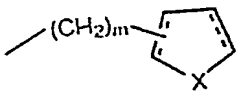


wherein n is 0 or 1;

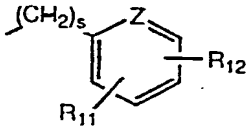
R_1, R_2, R_3, and R_4 are independently selected from hydrogen, hydroxy, amino, alkylamino, alkylsulfonylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge;

R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; and

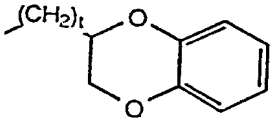
R_6 and R_8 are hydrogen and R_7 is



wherein m is 0, 1 or 2 and X is CH_2, O, S or $N-CH_3$; or R_7 is

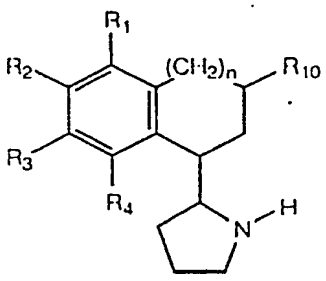


wherein s is 0, 1, or 2; Z is C or N; and R_{11} and R_{12} are independently selected from hydrogen, halo, hydroxy, methoxy, thiomethoxy, amino and loweralkyl, or R_{11} and R_{12} taken together can form a methylenedioxy or ethylenedioxy bridge; or R_7 is



wherein t is 0 or 1; or

R_6 is hydrogen and R_7 and R_8 taken together form a phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; comprising alkylating a compound of the formula

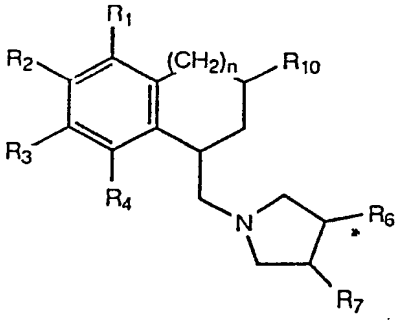


wherein n is 0 or 1;

R_1, R_2, R_3, and R_4 are independently selected from hydrogen, hydroxy, amino, alkylamino, alkylsulfonylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge; and

R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy.

13. A process for the preparation of a compound of the formula:

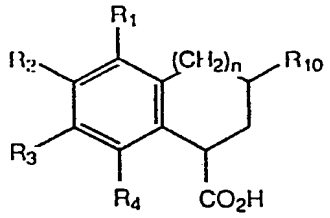


wherein n is 0 or 1;

R_1, R_2, R_3, and R_4 are independently selected from hydrogen, hydroxy, amino, alkylamino, alkylsulfonylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge;

R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; and

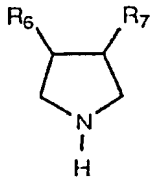
R_9 and R_6 are hydrogen and R_7 is phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or R_7 and R_9 are hydrogen and R_6 is benzyl, thienylmethyl, furylmethyl or substituted benzyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; comprising reacting a compound of the formula



wherein n is 0 or 1;

R_1, R_2, R_3, and R_4 are independently selected from hydrogen, hydroxy, amino, alkylamino, loweralkyl, loweralkoxy, halo, and thioalkoxy; or R_1 and R_2 or R_2 and R_3 taken together can form a methylenedioxy or ethylenedioxy bridge; and

R_{10} is hydrogen, loweralkyl, phenyl, or substituted phenyl wherein the the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or an acid chloride, ester or activated ester derivative thereof, with a compound of the formula



wherein R_6 is hydrogen and R_7 is phenyl, thienyl, furyl or substituted phenyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; or R_7 is hydrogen and R_6 is benzyl, thienylmethyl, furylmethyl or substituted benzyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, loweralkoxy, amino and thioalkoxy; followed by reduction of the resulting amide.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 89/00140

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): C07C 91/28; C07D 295/00; C07D 317/70

US. CL.: 546/270, 275, 281, 296, 299, 300, 307, 311, 334, 329, 115
548/518, 526, 561, 565, 566; 549/60, 74, 75, 336, 433, 492, 495

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.CL.:	546/270, 275, 281, 296, 299, 300, 307, 311, 334, 329, 115 548/518, 526, 561, 565, 566 549/60, 74, 75, 366, 492, 495

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

March, Advanced Organic Chemistry (2nd ed), 1977

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	U.S., A 3,419,560 (BERNSTEIN ET AL) 31 DEC. 1968 See entire document.	1-7
Y	U.S., A 3.704,323 (KRAPCHO) 28 NOV. 1972 entire document	1-7
Y	U.K., A 2,093,938 (DEBERNARDIS) 24 APRIL 1985 entire document	1-7
Y	March, Advanced Organic Chemistry 2nd ed (1977); McGraw-Hill Book Co; NY, Ny; pp. 382-385, 819	8-13
Y	Katritzky and Lagowski, The Principle of Heterocyclic Chemistry, (1968) Academic Press, New York, NY; P. 135	12, 13

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
13 March 1989 (13-03-89)	04 MAY 1989
International Searching Authority	**Signature of Authorized Officer**
ISA/US	MarySue Howard MarySue Howard (asst. examiner)

Form PCT/ISA/210 (second sheet) (Rev.11-87)